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# Cortisol and Externalizing Behavior in Children and Adolescents: Mixed Meta-Analytic Evidence for the Inverse Relation of Basal Cortisol and Cortisol Reactivity With Externalizing Behavior

***ABSTRACT:*** *An inverse relation between cortisol (re)activity and externalizing behavior has been hypothesized, but research findings seem equivocal. We tested this hypo(re)activity hypothesis in two meta-analyses, one for basal cortisol ($k = 72$ studies, $N = 5{,}480$) and one for cortisol reactivity to a stressor ($k = 29$ studies, $N = 2{,}601$). No association was found between cortisol reactivity and externalizing behaviors ($r = -.04$, 95% CI $= -.11, .02$). However, the relation between basal cortisol and externalizing behavior was significant but small ($r = -.05$, 95% CI $= -.10, -.002$). The age of the children significantly moderated this relation: Externalizing behavior was associated with higher basal cortisol (hyperactivity) in preschoolers ($r = .09$, 95% CI $= .002, .17$), and with lower basal cortisol (hypoactivity) in elementary school-aged children ($r = -.14$, 95% CI $= -.19, -.08$). There was no significant relation between cortisol and externalizing behavior in adolescents.* © *2008 Wiley Periodicals, Inc.* Dev Psychobiol 50: 427–450, 2008.

***Keywords:*** *cortisol; externalizing behavior; meta-analysis; children; adolescents*

## INTRODUCTION

In the past two decades, the study of child development has become an interdisciplinary area of research. Not only are researchers investigating environmental, behavioral, and psychological aspects of development, but genetic and biological factors have also made an entrance into the field. An area in which biological factors are being studied at an increasing rate is the development of behavior problems in children; in particular the biological correlates of externalizing behavior. One of the biological systems that have been the focus of research is the hypothalamic-pituitary-adrenal axis (HPA axis), with cortisol as its primary hormonal product in humans. Basal levels of cortisol have been examined as well as the change in cortisol levels in reaction to a stressor. Leading hypothesis is a negative relation between cortisol (re)activity and levels of externalizing behavior (e.g., Lahey, McBurnett, Loeber, & Hart, 1995; Van Goozen, 2005; Van Goozen, Fairchild, Snoek, & Harold, 2007). A number of studies reported this hypothesized hypo(re) activity of the HPA axis in children and adolescents with elevated levels of externalizing behavior, but findings so far have been equivocal. Results of studies associating cortisol reactivity with externalizing behavior are even

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more diffuse. The aim of the present study is to test the hypo(re)activity hypothesis in two separate meta-analyses, one for basal cortisol level and one for cortisol reactivity.

## The HPA Axis

The basic function of the stress system is to help the organism maintain homeostasis in an ever-changing environment. The stress system includes two components: the locus ceruleus/noradrenergic sympathetic system and the hypothalamic-pituitary-adrenal (HPA) axis (for an overview, see Gunnar & Quevedo, 2007). The first system reacts very quickly to threatening stimuli in the environment, whereas the HPA axis responds somewhat later and functions as a ''back-up'' and balancing system (Sapolsky, Romero, & Munck, 2000). This system can be considered a cascade of hormones influencing the release of other hormones. It starts in the paraventricular nucleus (PVN) of the hypothalamus, which releases corticotropin-releasing hormone (CRH) in response to activation by limbic, cortical, and other afferent inputs. In turn, CRH activates the production of adrenocorticotrophic hormone (ACTH) by the pituitary, which travels to the adrenal gland, and triggers the production of cortisol (Chrousos & Gold, 1992). When cortisol secretion reaches a certain level, it binds to glucocorticoid receptors (GRs) distributed throughout the brain that function to inhibit the production of CRH, ACTH, and cortisol, in order to return the system to a prestress or basal state (De Kloet, 1991; Sapolsky et al., 2000). Cortisol is also produced during normal, nonstress situations. These basal levels of cortisol normally follow a diurnal rhythm, with an increase in secretion of cortisol following awakening, followed by a decline throughout the rest of the day (Edwards, Clow, Evans, & Hucklebridge, 2001). This (low) basal HPA activity is regulated by (hippocampal) mineralcorticoid receptors (MRs). Individual differences exist in the functioning of every step in the cascade, including the sensitivity to these feedback signals (for a review on the effect of stress on the functioning of the HPA axis, see De Kloet, Joëls, & Holsboer, 2005).

The concept of allostasis is of much importance in current theorizing about HPA axis functioning. Allostasis, or maintaining stability through change, refers to a process of adaptation to challenge that maintains stability, or homeostasis, through an active process of change (McEwen, 1998; Sapolsky, 2004). However, if the system is challenged too heavily or too often, the cumulative cost of allostasis may disturb the balance of the system. This process is called allostatic load and may result in serious pathophysiology. For example, exposure to family adversity early in life may affect the balanced functioning of the child's neurobiological system and this may result in the development of psychological problems (Cicchetti, 2002; Susman, 2006).

## HPA Axis and Externalizing Behavior

Several studies hypothesized that lower basal cortisol levels and lower cortisol reactivity are associated with higher rates of externalizing behavior (e.g., Kariyawasam, Zaw, & Handley, 2002; McBurnett, Lahey, Capasso, & Loeber, 1996; Oosterlaan, Geurts, Knol, & Sergeant, 2005; Pajer, Gardner, Rubin, Perel, & Neal, 2001; Scerbo & Kolko, 1994; Schulz, Halperin, Newcorn, Sharma, & Gabriel, 1997; Van de Wiel, Van Goozen, Matthys, Snoek, & Van Engeland, 2004; Wright, 2000). There are a number of hypothesized mechanisms underlying the association between reduced HPA activity and antisocial behavior. One mechanism may be that people who are characterized by low autonomic arousal are predisposed to seek stimulation, for example, by fighting, to increase their low levels of arousal (Zuckerman, 1979). In turn, children who often seek stimulation and may therefore frequently be involved in dangerous and stressful situations may habituate to these stimuli and eventually show a blunted stress response (Van Goozen et al., 2007). The inverse relation between cortisol levels and externalizing behavior is also in line with the fearlessness theory formulated by Raine (1996). This theory claims that children showing high levels of externalizing behavior are less sensitive to stress and are less easily physiologically aroused than nonexternalizing children. As a result, they have low levels of anxiety and engage in outgoing, externalizing behavior more often.

Part of these mechanisms may be based on the functioning of the amygdala. This brain structure is considered to play a key role in the perception of threat signals in the environment (Amaral, 2003). When a stimulus is perceived as threatening or fearful, the amygdala activates the body's stress systems. The amygdala is also involved in learning the connection between a behavior and its consequences, such as punishment and reward (Holland & Gallagher, 1999). Damage to the amygdala or failure to activate it may result in a reduced stress response in reaction to fearful stimuli and may impede the ability to learn from punishment. In fact, there is some evidence for reduced fear behavior after amygdala lesions in primates (Kalin, Shelton, & Davidson, 2004).

The functioning of the HPA axis can be viewed both as cause and consequence of behavior, or alternatively both factors may result from an underlying cause. For example, McBurnett, King, and Scarpa (2003) argued that children with (aggressive) conduct problems are likely to have been exposed to prenatal and postnatal stress following from family circumstances, parenting, and parental characteristics (such as domestic violence, substance

abuse, low socioeconomic status, or parental depression). These early stressors may cause permanent alteration of the HPA axis and at the same time may be risk factors for the development of (externalizing) behavioral disorders. Illustrative of predominant biological perspectives on development however, is the view that hormones and behavior *mutually* influence each other and that this interaction can be both moderated and mediated by environmental factors (Susman & Ponirakis, 1997).

Not all empirical evidence regarding basal cortisol levels and reactivity in relation to externalizing behavior points in the same direction. For example, Van Bokhoven et al. (2005) concluded that basal levels of cortisol are positively related to aggression, and Hart, Burock, London, Atkins, and Bonilla-Santiago (2005) reported that enhanced basal cortisol and cortisol reactivity to a stressor were both associated with elevated levels of externalizing behavior, whereas McBurnett et al. (1996) found that lower basal cortisol levels were associated with higher levels of aggression. In addition, many studies presented nonsignificant relations between cortisol (reactivity) and externalizing behavior. In the next section we describe possible factors that may influence the relation between cortisol and externalizing behavior and therefore contribute to the divergence of empirical findings.

## Sample Moderators

***Clinical Versus Normal Samples.*** Cortisol levels and externalizing behavior have been assessed in children with clinical levels of problem behavior (e.g., Birmaher et al., 1994; McBurnett et al., 1996; Van de Wiel et al., 2004) and in normally developing children (e.g., Granger, Stansbury, & Henker, 1994; Hart et al., 2005; Tennes & Kreye, 1985). Clinical levels of problem behavior have been shown to be related to altered biological functions (Cicchetti & Walker, 2003; Goodyer, 2002; Keenan, 2000). Psychosocial and other biological risk factors (besides altered HPA axis functioning) are also inherently more often present in clinical groups than in typically developing groups of children (Cummings, Davies, & Campbell, 2000). Liu and Wuerker (2005) proposed a biopsychosocial model of aggressive and violent behavior in which biological and psychosocial factors interact in the development of aggressive behavior. Effects of biological factors (such as low cortisol production) may be moderated by other risk factors (e.g., socio-economical problems in the family, parental psychopathology) that are more often present in clinical groups. Consequently, a relation between cortisol levels and externalizing behavior might exist particularly in clinical groups.

***Age.*** Different outcomes of the studies may also be due to variety in age of the participants in the different studies. First, the frequency of externalizing behaviors changes with age. Several studies have shown an increase in infancy (Alink, Mesman, et al., 2006; Van Zeijl et al., 2006) and a decline in early and middle childhood (Prinzie, Onghena, & Hellinckx, 2006; Tremblay et al., 2004). Furthermore, it seems that HPA axis undergoes changes during development as well. It is argued that there are marked changes in the first years of life and early adolescence (see Gunnar & Quevedo, 2007). There is increasing evidence for a stress hyporesponsive period (SHRP) in early childhood. In this period it is difficult to produce elevations in cortisol levels. In humans the SHRP starts in the second half of the first year of life and extends over the childhood years (Gunnar & Quevedo, 2007). In addition, there is evidence that basal cortisol levels increase during late childhood and adolescence (reviewed in Gunnar & Vazquez, 2006). Because both the functioning of the HPA axis and the normative rate of externalizing behaviors change during development, the relation between those constructs may change with age as well.

***Gender.*** Many researchers have concluded that from toddlerhood or preschool-age onward, boys are more aggressive than girls (e.g., Alink, Mesman, et al., 2006; Tremblay et al., 1999). At the same time, some gender differences in level of cortisol have been found, although results of these studies are mixed. Increased activity of the HPA axis in response to stressors or physical exercise has been found for adult men compared to women (Kudielka, Buske-Kirschbaum, Hellhammer, & Kirschbaum, 2004; Putnam, Chrousos, Nieman, & Rubinow, 2005). In their review, Kudielka and Kirschbaum (2005) reported that studies investigating gender differences in cortisol responses in children reveal either no differences or heightened cortisol responses in boys. Results of studies addressing gender differences in basal cortisol are also mixed. Kudielka et al. (2004) reported no gender differences in basal cortisol in a sample consisting of older adults, younger adults, and children. However, Pajer, Gardner, Kirillova, and Vanyukov (2001) showed that boys had lower basal cortisol levels than girls. Since gender differences have been found for both level of externalizing behavior and level of cortisol, it is possible that differences also exist for the relation between these constructs. For example, Wright (2000) reported that cortisol reactivity was significantly related to aggression in girls but not in boys. Gender may thus moderate the association between cortisol and aggression.

## Procedural Moderators

***Cortisol Assessment and Type of Stressor.*** Across different studies cortisol was assessed in many different

types of situations and settings. For example, in several studies baseline cortisol was obtained upon arrival at the center as a prestressor measure and/or was obtained in an unfamiliar, potentially stressful situation (e.g., Jansen et al., 1999; Popma et al., 2006). It may be that children experienced (anticipatory) stress in these types of situations and as a result, the cortisol level that is obtained may not reflect true basal levels. In addition to (anticipatory) stress there are several other factors such as physical activity and food intake that may influence cortisol levels (Kirschbaum & Hellhammer, 1994). To reduce resulting error variance, it may be preferable to derive basal cortisol levels from multiple assessments. Since there is large variability in peak time after a stressor, multiple poststressor assessments would provide a better indication of reactivity than a single cortisol sample.

In addition, some stressors are more likely to evoke externalizing behaviors than others (e.g., social stressors such as a playgroup session with unfamiliar peers vs. a public speaking task). The effect of these social stressors on cortisol levels may depend on the child's level of externalizing behavior. For example, Lopez, Vazquez, and Olson (2004) noted that, when placed in a social setting, externalizing children may be more frequently engaged in stressful (aggressive) peer interactions than shy children. In addition, externalizing children are more likely to be rejected by peers because of their poor social skills. In turn, rejection is related to higher cortisol levels (Gunnar, Sebanc, Tout, Donzella, & Van Dulmen, 2003). As a result, behavioral differences may involve different levels of stress for externalizing and nonexternalizing children during peer interactions. Nonsocial stressors, such as individual testing, may thus be better for comparing HPA axis functioning between externalizing and nonexternalizing children. In addition, since peer interactions may increase cortisol levels in particular for highly externalizing children, assessing prestressor or basal cortisol levels after interaction with peers (e.g., at school) may not provide the best indicator for the true baseline levels of cortisol.

Other characteristics of the stressor may also moderate the relation between cortisol reactivity and externalizing behavior. On the basis of their meta-analysis, Dickerson and Kemeny (2004) concluded that two elements are necessary for a stressor to elicit a substantial response of the HPA axis in adults: outcome uncontrollability and social-evaluative threat. These factors may also be essential for cortisol reactions in children. When a stressor does not elicit substantial physiological stress responses in most children, any relation between behavior and cortisol reactivity will remain unnoticed. Consequently, it is possible that this relation is only identified when a relatively strong stressor (involving outcome uncontrollability and social-evaluative threat) has been used.

***Timing of Cortisol Assessment.*** The activity of the HPA axis normally follows a diurnal rhythm, which is established in humans in the first year of life (Gunnar & Donzella, 2002; Watamura, Donzella, Kertes, & Gunnar, 2004). This diurnal rhythm shows the highest levels approximately 30 min after wake-up, followed by a decline during the rest of the day (Edwards et al., 2001). Due to the diurnal rhythm, the level of cortisol is highly dependent on time of day of assessment and the relation of cortisol values to behavior may vary across times of day. Tout, De Haan, Campbell, and Gunnar (1998) for example found that morning and afternoon values showed different associations with child behavior.

A factor that is related to both time of day of sampling and situation of baseline sampling is the *law of initial value* (Lacey, 1956; Lewis & Ramsay, 1995a,b). This law denotes that reactivity of the HPA axis is related to the baseline value. According to this law, the cortisol reactivity to a stressor can be blunted when this baseline value is high (e.g., due to sampling in the morning or due to stress before or anticipation of the procedure). Consequently, results of studies addressing cortisol reactivity and externalizing behavior may depend on factors that influence the height of the baseline cortisol level (e.g., time of day of sampling and unintended or anticipatory stress before sampling).

***Cortisol Measures.*** Across all studies assessing cortisol, three different measures have been used: cortisol obtained from saliva, plasma, or urine. Salivary and urinary cortisol levels typically reflect the unbound or ''free'' fraction of the hormone, as opposed to plasma, reflecting total cortisol. Because it is the unbound cortisol that reaches the target tissue and elicits glucocorticoid effects (Kirschbaum & Hellhammer, 1994), this fraction is of most interest. Several studies have reported high correlations between salivary and plasma cortisol levels (ranging from $r = .54$ to $r = .97$; Kirschbaum & Hellhammer, 1989, 1994; Schwartz, Granger, Susman, Gunnar, & Laird, 1998), although absolute levels of cortisol found in saliva are much lower than cortisol levels in blood plasma. In contrast to salivary and plasma cortisol levels which reflect HPA activity at a certain time point, urinary cortisol levels reflect the integrated function of the HPA axis over a period of time. This difference probably accounts for the fact that Putignano et al. (2001) did not find a significant relation between salivary and urinary cortisol levels. Whereas cortisol assessment in saliva is a nonstressful, noninvasive technique, obtaining blood samples to assess plasma cortisol levels can be very stressful (and/or may cause anticipatory stress) and may therefore confound basal cortisol levels. With respect to saliva samples, another factor appears to compromise measurement of cortisol. In some studies, oral stimulants (e.g., powdered

drink mixes such as Kool-Aid) have been used. Schwartz et al. (1998) found that the use of oral stimulants may increase levels of cortisol and attenuate the relation between cortisol and behavior. More recently, Talge, Donzella, Kryze, Gierens, and Gunnar (2005) found that the use of oral stimulants did not affect the rank ordering of salivary cortisol values, although it did affect the level of the values, with the direction of effects depending on the type of assay. Therefore, using oral stimulants *within* a study when given to all participants will not affect the quality of the data, but the use of oral stimulants may compromise comparison *between* studies if they have been used in some studies but not in others.

***Assessment of Behavior: Observation or Questionnaires?*** Different methods have been used to assess level of externalizing behavior. A clear distinction can be made between questionnaires and observations. These methods may lead to differences in reported externalizing behavior (Karp, Serbin, Stack, & Schwarzman, 2004; McEvoy, Estrem, Rodriguez, & Olson, 2003). Independent observers are usually trained to adequate levels of intercoder reliability for observing the pertinent behavior of the children. When parents are asked to complete a questionnaire regarding their child's externalizing behavior, different parents may have varying interpretations of the items. On the other hand, observations are often short and take place in particular situations (such as laboratory settings), whereas parents base their report of the child's behavior on longer periods of time and various situations. The differences between levels of externalizing behavior assessed with independent observations or with questionnaires might result in differences in the relation between cortisol and externalizing behavior.

***Research Designs.*** Behavior and cortisol levels have not always been assessed at the same time point. Because both behavior and the HPA axis are susceptible to change (e.g., as a result of environmental factors), these differences in design (concurrent or nonconcurrent assessments) might account for differences in outcomes.

***Statistical Analyses.*** The distribution of cortisol values is often positively skewed. In several studies the raw data are therefore transformed (e.g., natural logarithm transformation; Azar et al., 2004; Oosterlaan et al., 2005), in others they are not. Moreover, a number of covariates are sometimes taken into consideration (e.g., time of day of cortisol sampling, demographic factors, or body mass). These different ways of treating cortisol data may account for differences in the relation between cortisol (reactivity) and behavior. Another difference between studies concerns the treatment of stressor data. Since the production of cortisol follows a diurnal rhythm and the amount of cortisol produced may vary between individuals it is important to measure the *change* in cortisol levels before and after a stressor. Results of analyses without a prestressor measure may not reflect an adequate estimation of the relation between cortisol reactivity and externalizing behavior. Therefore, this factor (whether a pretest measure was included in the reactivity analyses) was included in our meta-analysis of studies on cortisol reactivity and externalizing behavior.

## Moderators Based on Behavior

***Type of Externalizing Behavior.*** Externalizing behaviors refer to a group of behavioral characteristics that are considered to be undercontrolled and other-directed, such as antisocial, aggressive, oppositional, or overactive behaviors (Achenbach, 1991). From a clinical perspective, child externalizing behavior can be operationalized in terms of psychiatric diagnoses: disruptive behavior disorder (DBD; covering both conduct disorder [CD] and oppositional defiant disorder [ODD]) and attention deficit/hyperactivity disorder [ADHD; *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (*DSM-IV*); American Psychiatric Association, 1994]. There is some evidence that DBD and ADHD have different developmental backgrounds in terms of risk and protective factors (Lynam, 1996) and biological correlates (for a review, see Van Goozen et al., 2007). Therefore, the relation between cortisol and externalizing behavior may depend on the exact type of behavior that was assessed.

***Comorbidity.*** Externalizing problems in childhood are highly comorbid. Comorbidity may reflect the presence of two separate disorders, but may also be an indication of the presence of symptoms that fit more than one diagnosis, or of one disorder representing an early manifestation of another disorder (Caron & Rutter, 1991). According to Caron and Rutter the comorbid pattern may constitute a meaningful syndrome different from the ''pure'' diagnosis. There is strong comorbidity between the different types of externalizing problems or disorders (e.g., there is strong overlap between ADHD and CD; Hinshaw, Lahey, & Hart, 1993), but comorbidity with internalizing problems, such as depression or anxiety, is also common in childhood (for a review and meta-analysis, see Angold, Costello, & Erkanli, 1999). The relation between externalizing problems and biological factors may depend on the co-occurrence of internalizing problems. For example, McBurnett et al. (1991) have shown that children with both CD and anxiety disorder had higher levels of salivary cortisol than children with CD without comorbid anxiety disorder.

In sum, empirical evidence on the associations between basal cortisol levels and cortisol reactivity with externalizing behavior is equivocal despite two decades of increasing research efforts. In this article, we searched for convergence in study outcomes, as well as for explanations of divergence between findings. Substantial differences exist regarding the research methods and samples of studies investigating the associations of basal cortisol and cortisol reactivity with externalizing behavior in children and adolescents. We tested the relation of externalizing behavior with both baseline cortisol levels and cortisol reactivity in two meta-analyses and also examined whether differences in effect sizes were related to the inclusion of clinical versus nonclinical groups, age and gender of the participants, research design, assessment of behavior, quality of basal cortisol measure (whether the basal measures were assessed in a nonstressful familiar setting), setting of cortisol assessment (with or without peers), number of cortisol samples, time of cortisol sampling, cortisol measure (saliva, plasma, or urine), use of oral stimulants or not (in case of salivary cortisol), transformation of cortisol data versus use of raw data, use of covariates in analysis or not, type of stressor (in the meta-analysis on cortisol reactivity), quality of reactivity analyses (whether a baseline measure was taken into account), specific type of externalizing behavior, and comorbidity with internalizing problems.

## METHODS

### Literature Search

We systematically searched the electronic databases EconLit, ERIC, PAIS, PsychInfo, Science Citation Index Expanded, Social Sciences Citation Index, and Art and Humanities Citation Index with the key words *cortisol*, *hpa*, *adrenocortical*, or *neuroendocrine* combined with *externalizing*, *aggress** (the asterisk indicates that the search contained the word or word fragment; for example, key words were *aggression* or *aggressive*), *overactive*, *ODD*, *oppositional*, *CD*, *conduct disorder*, *ADHD*, *attention deficit hyperactivity disorder*, or *antisocial*. Second, the reference lists of the collected papers and dissertations were searched for relevant studies.

Studies were included if they reported on the relation between cortisol and the different types of externalizing behavior in children and adolescents (age range 0–19 years). If no adequate statistics were reported in the article, authors were contacted for additional details. Regarding studies on cortisol reactivity, we included studies using different kinds of psychological stressors, such as a public speaking task, a test, or playgroup sessions with unfamiliar teachers and peers. We did not include studies that reported on HPA-reactivity to a chemical challenge (e.g., dexamethasone).

We found 82 studies with 101 outcomes that were relevant to our meta-analyses, 59 studies with 72 outcomes concerning basal cortisol and 23 studies with 29 outcomes regarding cortisol reactivity, with sample sizes ranging from 16 to 369 (see Tab. 1).

### Inclusion of Studies in the Meta-Analyses

An overview of the studies that were included in the meta-analyses is presented in Table 1. Sixteen of the studies that assessed cortisol reactivity after a stressor also reported the relation between baseline cortisol and aggression. These studies were included in both meta-analyses.

Several studies presented data on (partly) overlapping samples. For example, McBurnett and colleagues published several articles concerning basal salivary cortisol and aggression in a group of 7- to 12-year-old children diagnosed with CD (McBurnett, 1989; McBurnett et al., 1996; McBurnett, Pfiffner, Capassi, Lahey, & Loeber, 1997; McBurnett, Lahey, Rathouz, & Loeber, 2000). Because in a meta-analysis studies should be independent, studies using the same sample of participants cannot be included in a meta-analysis more than once. The articles that reported on the largest groups of participants were included in our meta-analysis (e.g., McBurnett et al., 1996).

### Coding System

The coding system for characteristics of sample and study design is presented in Table 2. The variable ''quality of basal cortisol measure'' was only coded for studies on basal cortisol and ''stressor provoking aggression,'' ''type of stressor,'' and ''pretest cortisol included in reactivity analyses?'' were only coded for studies addressing cortisol reactivity. To assess intercoder reliability, ten randomly selected studies were coded by two coders. The agreement between the coders across the moderator variables was 100%.

### Meta-Analytic Procedures

Twelve studies reported results separately for boys and girls (Tab. 1). We calculated effect sizes for both subsamples. The two effect sizes computed for these subsamples were considered as independent outcomes in the analyses. When multiple measures of cortisol and/or externalizing behaviors were used within one study (e.g., McBurnett et al., 1996; Oosterlaan et al., 2005; Scerbo & Kolko, 1994; Schulz et al., 1997), we first conducted a meta-analysis within the study, and included the combined effect size in the final meta-analytic dataset. Within the domains of basal cortisol level and cortisol reactivity, every child was thus included only once in the meta-analyses.

Whereas most studies compared cortisol reactivity of externalizing and control groups or reported the correlation between cortisol and externalizing behavior, in four studies (with six study outcomes) cortisol increasers versus nonreactors (or decreasers) were compared regarding their scores on externalizing behavior (Klimes-Dougan, Hastings, Granger, Usher, & Zahn-Waxler, 2001; Scarpa & Kolko, 1996; Van de Wiel et al., 2004; Wright, 2000). For these studies *p*-values and sample sizes were used to compute effect sizes. Because this comparison may have resulted in different outcomes compared with the other studies, we used ''comparison of cortisol reactivity groups'' as a moderator in the meta-analysis concerning reactivity.

**Table 1. Studies Included in Meta-Analyses**

| Study | Basal/React | Sample size | % Boys | Age range | Clinical | Behavior | Cortisol measure | Stressor |
|---|---|---|---|---|---|---|---|---|
| Alink, Van IJzendoorn et al. (2006b) [a] | B + R | 70/79[b] boys, 60/76[b] girls | | 3.5 (2.1–2.4) | No | Aggression | Saliva | Strange Situation Procedure |
| Auton Cuff (2004) | B | 37 | 51 | (12–14) | No | Aggression | Saliva | — |
| Azar et al. (2004) | B | 170 | 0 | 17.2 | No | Aggressive CD | Saliva | — |
| Birmaher et al. (1994) | B | 37 | 38 | (11–18) | Yes | CD | Plasma | — |
| Blair, Granger, and Razza (2005) | B + R | 169 | 53 | 5.1 (3.8–5.7) | No | Aggression | Saliva | Testing session |
| Çakoloz, Akay, and Böber (2005) | B | 74 | 100 | 8.2 (6–11) | Yes | Aggression | Plasma | — |
| Cicchetti and Rogosch (2001) | B | 302 | 61 | 9.2 | Yes | Externalizing | Saliva | — |
| Cooper-Fenske, Gardner, and Pajer (2006) | R | 30 | 0 | (15–16) | Yes | CD | Plasma | Trier Social Stress Test |
| Dabbs, Jurkovic, and Frady (1991) | B | 113 | 100 | (17–18) | Yes | Delinquency | Saliva | — |
| De Haan, Gunnar, Tout, Hart, and Stansbury (1998) | B | 20 | 58 | 2.5 | No | Negative social behavior | Saliva | — |
| DeRose (2005) | B | 81 | 0 | (11–12) | No | Externalizing | Saliva | — |
| Dmitrieva, Oades, Hauffa, and Eggers (2001) | B | 41 | 100 | (10–18) | Yes | CD | Plasma | — |
| Essex et al. (2002) | B | 282 | 48 | 4.5 | No | Externalizing | Saliva | — |
| Fulgham (2003) | B | 67 | 100 | 5–7 | No | Aggression | Saliva | |
| Gerra et al. (1997) | B + R | 30 | 100 | 18.7 (18–19) | No | Aggression | Plasma | Free operant procedure to induce aggression |
| Gerra et al. (1998) [c] | B + R | 30 | 100 | 12.7 | No | Aggression | Plasma | Stroop color-word interference task, public speaking task |
| Gordis, Granger, Susman, and Trickett (2006) | R | 67 | 52 | 12.2 (10.0–14.5) | No | Aggression | Saliva | Trier Social Stress Test |
| Granda (1982) [a] | B | 21 boys, 17 girls | | 5 (3–6) | No | Aggression | Urine | — |
| Granger et al. (1998) | B + R | 62 | 42 | 6.7 (5–11) | No | Aggression | Saliva | Social interaction with mother (including conflict discussion) |
| Granger, Stasbury, and Henker, (1994) | B + R | 29 | 48 | 4.7 (3.6–6.7) | No | Aggression | Saliva | Playgroup sessions with unfamiliar teachers and peers |
| Granger et al. (1994b) Granger, Weisz, and Kauneckis (1994) | R | 102 | 61 | 12.1 (7.0–17.8) | Yes | Aggression | Saliva | Parent-child conflict discussion task |
| Grayson (2001) | B | 26 | 100 | (9–11) | No | Aggr. | Saliva | — |
| Gunnar et al. (2003) [a] | B | 76 (55% boys)[f] | | 4.0 (3–5) | No | Aggr. | Saliva | — |
| Gunnar, Tout, De Haan, Pierce, and Stansbury (1997) study 1 | B | 26 | 54 | 4.3 (3.1–5.2) | No | Frustrated aggr. | Saliva | — |
| Gunnar et al. (1997) study 2 | B | 46 | 70 | 4.2 (3.2–5.2) | No | Aggr./anger | Saliva | — |
| Hart (1999) | B | 103/49[d] | 65 | 9.2/9.0 | No | Ext | Saliva | — |
| Hart et al. (2005) | B + R | 61 | 46 | 11.5 | No | Ext | Saliva | Standardized tests at school |
| Hart, Gunnar, and Cicchetti (1995) | B | 33/16[d] | 79 | (3.9–6.3)/(2.3–4.9) | No | Acting out/ext. | Saliva | — |

(*Continued*)

**Table 1.** (*Continued*)

| Study | Basal/React | Sample size | % Boys | Age range | Clinical | Behavior | Cortisol measure | Stressor |
|---|---|---|---|---|---|---|---|---|
| Hruschka, Kohrt, and Worthman (2005) | B | 29 | 100 | (6.5–8.0) | No | Aggr. | Saliva | — |
| Jansen et al. (1999) | B + R | 29 | 76 | 10.0 | Yes | CD/ODD | Saliva | Continuous Performance Task and four neuro-psychological tests (separate sessions) |
| Kariyawasam, Zaw, and Handley (2002) | B | 33 | 89 | 11 | Yes | ADHD/ODD | Saliva | — |
| Klimes-Dougan et al. (2001) [a] | B + R | 74/96[b] boys, 78/96[b] girls | | 13.7 (11–16) | No | Ext | Saliva | Social performance paradigm |
| Kruesi et al. (1989) | B | 38 | 100 | (7–16) | Yes | CD, ODD, and/or ADHD | Urine | — |
| Locke (2005) [a] | B + R | 144/146[b] boys, 157/158[b] girls | | 8.3 (6–10) | No | Anger | Saliva | Three Lab-TAB episodes, emotion-modulated startle paradigm, challenging math task |
| Loney, Butler, Lima, Counts, and Eckel (2006) [a] | B | 30 boys, 29 girls | | (12–18) | No | CD/ODD | Saliva | — |
| Lopez (2005) | B + R | 51 | 55 | (6–7) | No | Aggr. | Saliva | Exposure to rubber snake or opening box that could not be opened (different conditions) |
| Luby, Mrakotsky, Heffelfinger, Brown, and Spitznagel (2004) | R | 102 | 48 | (3.0–5.6) | Yes | ADHD/ODD | Saliva | Structured play tasks from Laboratory Temperament Assessment Battery, separation from parent |
| Maldonado et al. (2006) | B + R | 68 | 56 | 5–7 | Yes | ADHD | Saliva | Trier Social Stress Test |
| McBurnett et al. (1996) | B | 53 | 100 | 9.6 (7–12) | Yes | Aggr. CD | Saliva | — |
| McBurnett et al. (2005) | B + R | 290 | 100 | 16.2 (14.2–18.8) | No | Conduct problems | Saliva | Trier Social Stress Test |
| Montagner et al. (1978) | B | 33 | 50 | (2–5) | No | Aggr. | Urine | — |
| Moss, Vanyukov, and Martin (1995) | R | 184 | 100 | (10–12) | No | Aggressive delinquency | Saliva | Event-related potential task |
| Oosterlaan et al. (2005) | B | 25 | 84 | 9.2 (6–12) | Yes | Aggr. CD | Saliva | — |
| Pajer, Gardner, Kirillova, et al. (2001) [a] | B + R | 369 boys, 91 girls | | 11.3/11.6 | No | Disinhibition | Saliva | Event-related potential task |
| Pajer, Gardner, Rubin, et al. (2001) | B | 47 | 0 | 16.3 (15–17) | Yes | Aggr. CD | Plasma | — |
| Popma et al. (2006) | B + R | 51 | 100 | 13.5 (12–14) | Yes | DBD | Saliva | Psychosocial stress test |
| Scarpa and Kolko (1996) | R | 17[e] | 89 | 7–15 | Yes | Aggr. | Saliva | Provocation task |
| Scerbo and Kolko (1994) | B | 40 | 93 | 11.2 (7–14) | Yes | Aggr. | Saliva | — |
| Schiefelbein (2005) [a] | B | 42 boys, 46 girls | | 11.4 (9–13), 10.6 (8–12) | No | CD/ODD | Saliva | — |
| Schulz et al. (1997) | B | 50 | 100 | (7–11) | Yes | Aggr. | Plasma | — |
| Shirtcliff, Granger, Booth, and Johnson (2005) [a] | B | 277 boys, 253 girls | | (10–16) | No | Ext | Saliva | — |
| Smider et al. (2002) | B | 172 | 49 | 4.5 | No | Ext | Saliva | — |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Snoek, Van Goozen, Matthys, Buitelaar, and van Engeland (2004) | B + R | 41 | 78 | 10.2 | Yes | ODD | Saliva | Competitive setting inducing frustration, provocation, and aggression |
| Snoek et al. (2002) | B | 35 | 63 | 10.4 (7–12) | Yes | ODD | Saliva | — |
| Stoff et al. (1992) | B | 16 | 100 | 15.0 | Yes | DBD | Plasma | — |
| Susman, Granger, Murowchick, Ponirakis, and Worrall (1996)[a] | B | 56 boys, 52 girls | | 12.7 (10–15), 11.9 (9–15) | No | Ext | Plasma | — |
| Susman and Ponirakis (1997) | B | 78 | 0 | (13–19) | No | CD | Saliva | — |
| Tennes and Kreye (1985) | B | 30 | 54 | 6.9–9.0 | No | Aggr. | Urine | — |
| Tout et al. (1998) | B | 38 boys, 37 girls | | 4.3 (2.7–5.8) | No | Aggr. | Saliva | — |
| Van Bokhoven et al. (2005) | B | 61 | 100 | 13 | No | Aggr. CD | Saliva | — |
| Van de Wiel et al. (2004) | B + R | 22 | 100 | 10.3 (8–13) | Yes | Aggr. | Saliva | Competitive setting including frustration, provocation, and aggression |
| Van Goozen et al. (1998) | B | 52 | 100 | 9.9 (8–11) | Yes | Aggr. | Saliva | — |
| Vanyukov et al. (1993) | B | 150 | 100 | (10–12) | No | CD | Saliva | — |
| Weizman et al. (1987) | B | 32 | 81 | 8.8 (6–11) | Yes | ADHD | Plasma | — |
| White and Mulligan (2005) | B | 33 | 81 | 8.3 (5–13) | Yes | ADHD | Saliva | — |
| Wright (2000) [a] | R | 26 boys, 29 girls | | 13.4 | No | Aggr. | Saliva | Trier social stress test |

*Note*: Sample size as included in meta-analyses.

ADHD, attention deficit hyperactivity disorder; CD, conduct disorder; DBD, disruptive behavior disorder; ODD, oppositional defiant disorder.

[a] Results were presented separately for boys and girls and were used independently in the meta-analyses.

[b] Sample sizes for basal/reactivity.

[c] Mean statistics for comparison of cortisol reactivity of the high aggression group to the medium and low aggression groups were used. Half of the sample size of the high aggression group was used for both statistics.

[d] Sample size for maltreated children/nonmaltreated, separate effect sizes for both groups.

[e] This sample size is based on the degrees of freedom reported for the *t*-test for comparing abused cortisol reactors to nonreactors. However, considering the overall *N*, this sample size of the abused group seems unlikely. A *t*-test was only conducted for the abused groups. No statistics were presented for comparison of the nonabused groups regarding aggression scores.

[f] The number of boys in the final sample is not given. However, 55% of the original sample ($N = 82$) were boys. Based on this percentage, we estimated the number of boys in the final sample on 42.

**Table 2. Coding System for Studies on Cortisol and Externalizing Behavior**

| Variable | Coding system |
|---|---|
| Sample | |
| Age of children at cortisol sampling | 1 = 0–5 years<br>2 = 5–12 years<br>3 = 12–19 years |
| Children clinically referred or meeting DSM criteria? | 0 = no<br>1 = yes |
| Gender of children in sample | 1 = mainly boys (>80%)<br>2 = mixed<br>3 = mainly girls (>80%) |
| Design | |
| Research design | 1 = concurrent assessment cortisol and aggression<br>2 = nonconcurrent assessment cortisol and aggression |
| Behavior observed? | 0 = no, only questionnaires and/or interviews<br>1 = yes, at least one of the measures was observation |
| Quality of basal cortisol measure | 0 = not optimal<br>1 = good |
| Baseline cortisol assessment in setting with peers? | 0 = no<br>1 = yes |
| Number of cortisol samples basal | 1 = 1<br>2 = 2–5<br>3 = >5 |
| Number of cortisol samples reactivity | 0 = no pretest, 1 or more posttest<br>1 = 1 pre, 1 post<br>2 = ≥1 pre and ≥ post |
| Time of cortisol sampling | 1 = morning<br>2 = (after)noon<br>3 = varied |
| Stressor provoking aggression? | 0 = no<br>1 = yes |
| Type of stressor | 1 = weak<br>2 = strong (uncontrollable outcome and social-evaluative threat) |
| Pretest cortisol included in reactivity analyses? | 0 = no<br>1 = yes |
| Cortisol measure | 1 = saliva<br>2 = plasma<br>3 = urine |
| Oral stimulants used (in case of saliva)? | 0 = no<br>1 = yes |
| Cortisol data transformed? | 0 = no<br>1 = yes |
| Covariates used in analyses? | 0 = no<br>1 = yes |
| Comparison of cortisol reactivity groups? | 0 = no (comparison of externalizing groups, or correlations)<br>1 = yes |
| Type of behavior | |
| Behavior | 1 = externalizing<br>2 = aggression<br>3 = DBD<br>4 = ADHD (in combination with CD and/or ODD)<br>5 = other |
| Comorbid with internalizing? | 0 = no<br>1 = yes |

### Statistical Analyses

Two meta-analyses were conducted, one for the relation between basal levels of cortisol and externalizing behavior and one for the relation between change in levels of cortisol in response to a stressor and externalizing behavior. The meta-analyses were performed using the Comprehensive Meta-Analysis (CMA) program (Borenstein, Rothstein, & Cohen, 2005, Version 2). For each study, an effect size (correlation) was calculated. Effect sizes indicating a positive relation between basal cortisol or cortisol reactivity and externalizing behavior were given a positive sign (higher basal cortisol levels/higher poststressor than prestressor levels associated with higher externalizing rates, or larger cortisol increase or smaller decrease in the externalizing group compared to the control group). When effect sizes indicated a negative relation between basal cortisol or cortisol reactivity and externalizing behavior, they were given a negative sign (lower basal cortisol levels/lower poststressor than prestressor levels associated with higher externalizing rates, or smaller cortisol increase or larger decrease in the externalizing group compared to the control group).

Using CMA, combined effect sizes were computed. Significance tests and moderator analyses were performed through fixed or random effects models, depending on the homogeneity of the study outcomes. Fixed effects models are based on the assumption that effect sizes observed in a study estimate the corresponding population effect with random error that stems only from the chance factors associated with subject-level sampling error in that study (Lipsey & Wilson, 2001; Rosenthal, 1995). This assumption is not made in random effects models (Hedges & Olkin, 1985). Random effects models allow for the possibility that there are random differences between studies that are associated with variations in procedures, measures, settings, that go beyond subject-level sampling error, and thus point to different study populations (Lipsey & Wilson, 2001). Whether fixed or random models can be used depends on the homogeneity of the set of effect sizes. To test the homogeneity of the overall and specific sets of effect sizes, we computed $Q$-statistics (Borenstein et al., 2005). In addition, we computed 95% confidence intervals (CIs) around the point estimate of each set of effect sizes. When the set was homogeneous, CIs were based on fixed estimates. In case of heterogeneity of the set, we based CIs on random estimates. $Q$-statistics and $p$-values were also computed to assess differences between combined effect sizes for specific subsets of study effect sizes grouped by moderators. Again, fixed effects model tests were used in the case of homogeneous sets of outcomes, and more conservative random effects model tests were used in the case of heterogeneous outcomes. In the present study random models were tested unless otherwise specified. Contrasts were only tested when at least two of the subsets consisted of at least four studies (Bakermans-Kranenburg, Van IJzendoorn, & Juffer, 2003).

Funnel plots for both sets of studies were examined in order to detect possible publication bias. A funnel plot is a plot of each study's effect size against its standard error (usually plotted as 1/SE, or precision). It is expected that this plot has the shape of a funnel, because studies with smaller sample sizes (larger standard errors) have increasingly large variation in estimates of their effect size as random variation becomes increasingly influential, whereas studies with larger sample sizes have smaller variation in effect sizes (Duval & Tweedie, 2000b; Sutton, Duval, Tweedie, Abrams, & Jones, 2000). However, smaller studies with nonsignificant results or with effect sizes in the nonhypothesized direction are less likely to be published. Therefore, a funnel plot may be asymmetrical around its base. The degree of asymmetry in the funnel plot was examined by estimating the number of studies which have no symmetric counterpart on the other side of the funnel. The ''trim and fill'' method was used to test the influence of possible adjustments of the sets of studies for publication bias (Duval & Tweedie, 2000a,b).

For each study, Fisher's $Z$ scores were computed as equivalents for correlations. Fisher's $Z$ scores have better distribution characteristics than correlations, in particular better estimates of the standard error (Mullen, 1989; Lipsey & Wilson, 2001). No outliers (standardized $z$-values smaller than $-3.29$ or larger than 3.29; Tabachnik & Fidell, 2001) were found for study effect size computed as Fisher's $Z$s. Fisher's $Z$ scores were used in the weighted least squares regression analyses to test the effects of the continuous variables age, gender, and number of cortisol samples. Due to the relatively small numbers of studies and participants in the set of studies on cortisol reactivity, we did not perform these regression analyses for cortisol reactivity. In addition, in a multivariate approach we investigated whether the effects of the significant sample-related moderators were still significant after controlling for the study design characteristics and the other sample-related moderators. To reduce the relatively large number of covariates in proportion to the relatively small number of studies, we computed an index for the overall quality of study design. The number of favorable design characteristics of each study was counted. Favorable design characteristics were: concurrent assessment of cortisol and behavior, good quality of basal cortisol measure, cortisol assessment in situations without peers, cortisol assessment at same time of day (morning or afternoon) for all participants, assessment of salivary cortisol instead of urine or plasma cortisol, and transformation of skewed cortisol data. The index for quality of design was used as a variable in the multivariate analyses on the effect sizes for basal cortisol reported below.

## RESULTS

### Basal Cortisol Levels

The meta-analysis concerning the relation between basal levels of cortisol and externalizing behavior included 59 studies with 72 study outcomes. Data were presented for 5,480 children. The combined effect size for the relation between basal cortisol and externalizing behavior was small but significant ($r = -.05$, 95% CI $= -.10$, $-.002$, $p < .05$) in a heterogeneous set of studies ($Q = 185.94$, $p < .01$). Overall, lower levels of cortisol were related to higher levels of externalizing behavior. Using the trim and fill method (Duval & Tweedie, 2000a,b), no asymmetry was found in the funnel plot, therefore evidence for publication bias was absent. The

fail-safe number for this set of studies was 140. It would take 140 null results to cancel out this significant combined effect size.

We tested whether moderators regarding sample characteristics (age, whether or not the sample consisted of clinical participants, and gender) were associated with effect size (Tab. 3). The contrast for age group was significant ($Q[2,68] = 20.83$, $p < .01$). The 31 studies focusing on school-aged children ($n = 2,407$) showed the largest combined effect size in the hypothesized direction ($r = -.14$, $p < .01$). The combined effect size for the sets of studies with samples consisting of children younger than 5 years of age ($k = 18$, $n = 1,145$) was also significant, but in the opposite direction ($r = .09$, $p < .05$). For the sets of studies with adolescent samples ($k = 19$, $n = 1,742$) and with samples with a broad age range ($k = 4$, $n = 180$) the combined effect sizes were not significant ($r = -.01$, $p = .84$; and $r = -.15$, $p = .17$, respectively). The effect size for studies focusing on children between 5 and 12 years of age was significantly different from the effect size for the set of studies investigating the youngest ($Q[1,47] = 18.01$, $p < .01$) and oldest groups ($Q[1,48] = 7.41$, $p < .01$). The effect size for the youngest age groups differed also significantly from that for the set of studies with a broad age group (using a fixed effects model, $Q[1,20] = 11.42$, $p < .01$). Thus, lower cortisol levels (hypoactivity) were associated with higher levels of externalizing behavior in studies investigating school-aged children and with lower levels of externalizing behavior in studies on preschoolers, whereas this relation was not significant in studies that investigated adolescents or groups of children with a broad age range. We also tested whether the relation between age as a *continuous* variable and Fisher's $Z$ revealed a similar pattern. The linear (centered) and the quadratic terms were both entered in a weighted least squares regression model (Lipsey & Wilson, 2001) predicting Fisher's $Z$ scores. In this analysis Fisher's $Z$ was weighted for the inverse variance in order to give studies with larger sample sizes more weight in the analyses. Significance tests were based on corrected standard errors (Lipsey & Wilson, 2001). Studies with a broad age group were excluded from this analysis. Multiple $R$ of the model was .33 ($p < .01$). The effect for the quadratic term of age was significant, $\beta = .33$, $p < .01$, thus confirming the results of the analyses with age as a categorical variable. Figure 1 shows the quadratic relation between age and Fisher's $Z$.

Next, the effect of clinical status was investigated. The combined effect size for the set of studies involving children with clinical levels of problem behavior ($k = 22$, $n = 1,232$) was significant ($r = -.10$, $p < .05$), but this effect size did not differ significantly from that for the studies assessing typically developing children ($k = 50$, $n = 4,248$), $Q(1,70) = 1.41$, $p = .24$ (Tab. 3). In addition, the combined effect size for studies investigating mainly boys ($k = 34$, $n = 2,519$) was significant ($r = -.09$, $p < .01$), but the effect sizes for the three sets of studies with different proportions of boys and girls did not differ significantly ($Q[2,69] = 4.03$, $p = .13$). The same was true for the different comparisons between two sets within these three subsets. These findings were confirmed by the results of a weighted regression analysis with gender (percentage of boys) as a continuous variable.

We also tested whether characteristics of study design (concurrent vs. nonconcurrent research design, behavior observed or not, quality of basal cortisol measure, number of cortisol samples, setting of cortisol assessment, time of cortisol sampling, cortisol measure, use of oral stimulants or not, transformation of cortisol data vs. use of raw data, and use of covariates in analysis or not) were associated with effect size. Several combined effect sizes for subsets of studies were significant (Tab. 3): studies with a concurrent research design ($r = -.06$, $p < .05$), externalizing behavior assessed with questionnaires ($r = -.07$, $p < .05$), cortisol assessed in a situation with no peers present ($r = -.07$, $p < .05$), cortisol assessed in plasma ($r = -.13$, $p < .05$), transformation of cortisol data ($r = -.07$, $p < .05$), and studies that did not include covariates in the analyses ($r = -.06$, $p < .05$). However, effect sizes for these subsets did not differ significantly from the effect sizes of the other subset(s) within the particular moderator (Tab. 3). The results of the weighted regression analysis for number of cortisol samples confirmed the findings in CMA: There was no significant relation between Fisher's $Z$ and number of cortisol samples. Two studies were excluded from this analysis because of lack of information about the exact number of cortisol samples (Granda, 1982; Kruesi, Schmidt, Donnelly, Hibbs, & Hamburger, 1989).

Next, effect sizes were computed separately for studies measuring different types of externalizing behavior problems (Tab. 3). The only subset for which the correlation was significant was the ''other'' category in which behaviors delinquency, negative social behavior, anger, and disinhibition were included ($r = -.11$, $p < .05$). The combined effect sizes for the different subsets of studies did not differ significantly ($Q[4,67] = 3.24$, $p = .52$). The effect of the moderator ''comorbid with internalizing problems'' could not be tested because there were only two effect sizes for the combination of internalizing and externalizing problems. The effect size in the subset of studies that did not include internalizing problems was significant, but this subset consisted of 70 of the total set of 72 studies. Therefore, the role of comorbidity with internalizing problems remains unclear.

**Table 3. Meta-Analytic Results of Studies Relating Basal Cortisol and Externalizing Behavior**

| Characteristics | *k* | *n* | *r* | 95% CI | $Q^a$ | *p* |
|---|---|---|---|---|---|---|
| Total set | 72 | 5,480 | −.05* | −.10, −.002 | 185.94 | .00 |
| Sample | | | | | | |
| Clinical | | | | | 1.41 | .24 |
| No | 50 | 4,248 | −.03 | −.08, .02 | 126.44** | |
| Yes | 22 | 1,232 | −.10* | −.19, −.001 | 55.42** | |
| Age | | | | | 20.83 | .00 |
| 0–5 years | 18 | 1,145 | .09* | .002, .17 | 26.34 | |
| 5–12 years | 31 | 2,407 | −.14** | −.19, −.08 | 56.32** | |
| 12–19 years | 19 | 1,742 | −.01 | −.08, .09 | 49.47** | |
| Broad | 4 | 186 | −.15 | −.35, .07 | 6.38 | |
| Gender | | | | | 4.03 | .13 |
| Mainly boys | 34 | 2,519 | −.09** | −.15, −.02 | 80.96** | |
| Mixed | 23 | 1,731 | .02 | −.06, .10 | 55.50** | |
| Only girls | 15 | 1,230 | −.07 | −.16, .02 | 31.77** | |
| Study design | | | | | | |
| Research design | | | | | 1.86 | .17 |
| Concurrent | 61 | 4,258 | −.06* | −.12, −.01 | 146.26** | |
| Nonconcurrent | 11 | 1,222 | .02 | −.09, −.13 | 28.82** | |
| Behavior observed? | | | | | 2.33 | .13 |
| No | 57 | 4,536 | −.07* | −.12, −.01 | 151.80** | |
| Yes | 15 | 944 | .02 | −.08, .12 | 27.75* | |
| Quality basal cortisol | | | | | .01 | .94 |
| Not optimal | 57 | 3,691 | −.05 | −.11, .01 | 138.81** | |
| Good | 15 | 1,789 | −.05 | −.14, .05 | 46.09** | |
| Setting cortisol assessment | | | | | 2.18 | .14 |
| Without peers | 52 | 4,252 | −.07* | −.12, −.01 | 146.35** | |
| With peers | 20 | 1,228 | .01 | −.08, .10 | 34.61* | |
| Number of cortisol samples | | | | | 1.73 | .42 |
| 1 | 33 | 2,035 | −.07 | −.15, .01 | 92.29** | |
| 2–5 | 20 | 2,593 | −.05 | .13, .03 | 71.29** | |
| >5 | 19 | 852 | −.002 | −.08, .07 | 20.01 | |
| Time of cortisol sampling | | | | | .40 | .82 |
| Morning | 28 | 2,541 | −.07 | −.14, .01 | 76.11** | |
| (After)noon | 17 | 1,078 | −.03 | −.14, .09 | 49.99** | |
| Varied | 27 | 1,861 | −.05 | −.12, .02 | 51.53** | |
| Cortisol measure | | | | | 2.07 | .35 |
| Saliva | 56 | 4,876 | −.04 | −.09, .01 | 152.29** | |
| Urine | 5 | 139 | .05 | −.20, .29 | 8.53 | |
| Plasma | 11 | 465 | −.13* | −.25, −.001 | 18.25* | |
| Oral stimulants used? | | | | | .27 | .60 |
| No | 37 | 3,847 | −.04 | −.10, .03 | 127.67** | |
| Yes | 19 | 1,029 | −.06 | −.14, .02 | 23.62 | |
| Cortisol data transformed? | | | | | .32 | |
| No | 45 | 2,478 | −.04 | −.11, .03 | 118.55** | |
| Yes | 27 | 3,002 | −.07* | −.13, −.002 | 67.10** | |
| Covariates used in analyses? | | | | | .17 | .68 |
| No | 50 | 3,295 | −.06* | −.11, −.01 | 102.45** | |
| Yes | 22 | 2,185 | −.04 | −.13, .05 | 78.04** | |
| Behavior | | | | | 3.24 | .52 |
| Externalizing | 16 | 2,179 | −.06 | −.15, .02 | 54.61** | |
| Aggression | 32 | 1,578 | −.05 | −.13, .04 | 77.97** | |
| DBD | 13 | 625 | .02 | −.11, .16 | 30.74** | |
| ADHD (+ODD/CD) | 5 | 204 | −.11 | −.27, .06 | 6.56 | |
| Other | 6 | 894 | −.11* | −.21, −.02 | 8.53 | |

(*Continued*)

**Table 3.** (*Continued*)

| Characteristics | *k* | *n* | *r* | 95% CI | $Q^a$ | *p* |
|---|---|---|---|---|---|---|
| Comorbid with internalizing[b] | | | | | | |
| No | 70 | 5,328 | −.05* | −.10, −.003 | 185.59** | |
| Yes | 2 | 152 | .00 | −.16, .16 | | |

*Note*: *k*, number of studies; *n*, total number of participants; CI, confidence interval.
*$p < .05$.
**$p < .01$.
[a]*Q* statistic for moderator stands for effect of contrasts (df = number of subgroups − 1), *Q* statistic for subgroup stands for homogeneity (df = $k - 1$).
[b]One or more of the subgroups consist(s) of less than four studies. Therefore, this/these group(s) was/were excluded from the contrast analyses, or in case of only two subsets, the effect of this moderator could not be tested.

***Moderator Tests Within the Age Groups.*** Since the direction of effect sizes differed between age groups, the effect of the moderators within each age group might differ as well. Therefore, we tested the effect of the moderators with a significant effect size in at least one of the subgroups (in the total sample) within the three different age groups (excluding the subset with broad ages). First, we tested the effect of the moderator clinical status within the age groups. Studies focusing on children younger than 5 years of age with clinical levels of problem behavior were absent. Effect sizes for all subgroups except for the clinical and nonclinical adolescents were significant (Fig. 2). However, within the sets of studies focusing on either school-aged children or adolescents effect sizes for clinical and nonclinical studies did not differ significantly.

In addition, we tested the effect of the moderators gender, research design, behavior observed, cortisol assessed in a setting with peers, cortisol measure, cortisol data transformed, covariates used in analyses, and type of behavior within the three different age groups. None of the moderator effects were significant, indicating that within the different age groups these variables did not influence the relation between basal cortisol and externalizing behavior, which was similar to the role of these moderators in the total set of studies.

***Multivariate Approach.*** To test whether age was associated with effect size after controlling for quality of study design (see Methods section), number of cortisol samples, clinical status (whether or not clinical participants were included), and gender in a more systematic way, a weighted least squares multiple regression analysis was conducted. The dependent variable was Fisher's *Z* for study outcomes. Independent variables were age (the broad age category was excluded), clinical status, gender (percentage of boys), number of cortisol samples (two studies with lack of information about the exact number of

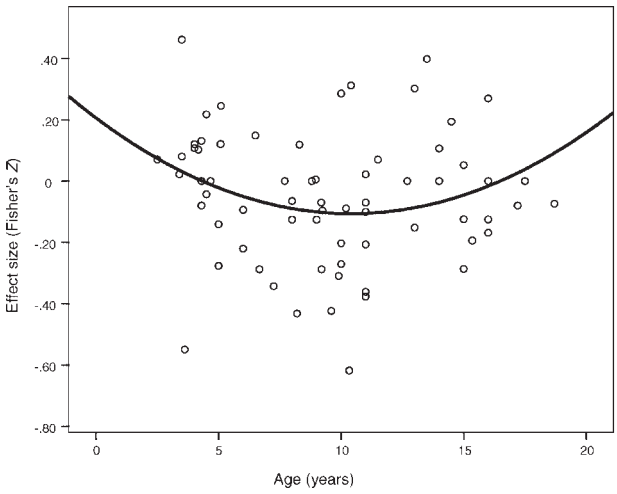


**FIGURE 1** The quadratic relation between age and Fisher's *Z* in the set of studies on basal cortisol.

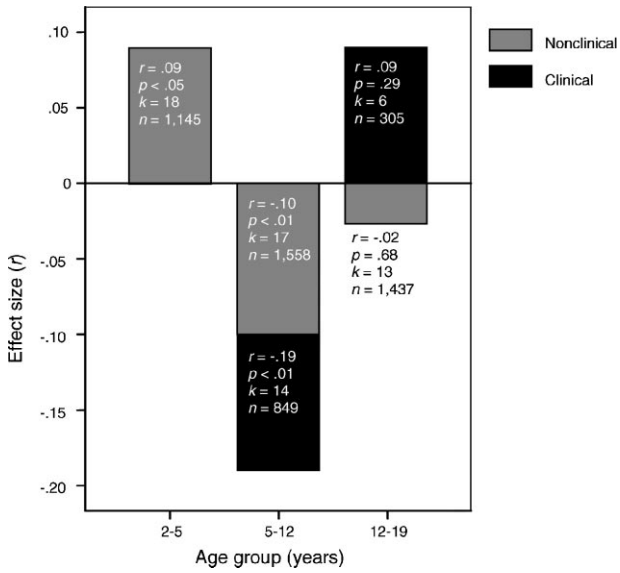


**FIGURE 2** Effect sizes for groups based on age and clinical status in the set of studies on basal cortisol.

cortisol samples were excluded) and quality of study design. Because the effect of age group was nonlinear, the squared term of this variable was also entered. To avoid multicollinearity, the centered term of age group was used in the analysis (Aiken & West, 1991). Multiple $R$ was .41 ($p < .01$). The effects of the quadratic term of age ($\beta = .26$, $p < .01$), clinical status ($\beta = -.17, p < .01$), and quality of study design ($\beta = -.24$, $p < .01$) were significant. Significance tests were based on corrected standard errors (Lipsey & Wilson, 2001). Age showed a significant curvilinear association with effect sizes across studies, independently of the other predictors such as quality or clinical status.

## Cortisol Reactivity

We found 23 studies with 29 study outcomes reporting a relation between cortisol reactivity to a stressor and level of externalizing behavior. Data were reported for 2,601 children. Overall, the combined effect size was not significant ($r = -.04$, 95% CI $= -.11$, .02, $p = .19$; Tab. 4). The set of studies was heterogeneous ($Q = 65.87$, $p < .01$). Cortisol reactivity was not significantly related to externalizing behavior in the total set of samples. Using the trim and fill method (Duval & Tweedie, 2000a,b), no studies appeared to be symmetrically unmatched. Hence, evidence for publication bias was absent.

We tested whether age group, clinical status, and gender were associated with effect size. For age group we excluded the subgroup with broad age ranges when contrasts were tested because there were fewer than four studies in this subset. None of the combined effect sizes of the subsets regarding age group, clinical status, and gender were significant (Tab. 4). In addition, within these moderators the combined effect sizes for the subgroups did not differ significantly.

We also investigated whether study design characteristics were related to differences among effect sizes. The following contrasts could be tested (because at least two subsets consisted of at least four studies): behavioral measure (whether or not observations were used), number of cortisol samples, time of cortisol sampling, stressor provoking aggression or not, type of stressor, use of oral stimulants in case of saliva collection, transformation of cortisol data, use of covariates in the analyses, pretest included in analysis, and comparison of cortisol reactivity groups. Only the effect size for the subset of studies in which the cortisol data were transformed was significant ($r = -.07$, $p < .05$), but the effect size for this subset did not differ significantly from that for the subset that analyzed the raw data ($Q[1,27] = .84$, $p = .36$).

None of the other effect sizes for the different subgroups based on these design characteristics were significant. Additionally, the other contrasts that could be tested were not significant. Moreover, the combined effect size of the subset of studies in which either a correlation between cortisol reactivity and level of externalizing behavior, or a comparison between high and low externalizing groups was reported ($r = -.05$, $p = .20$) did not differ significantly from that of the subset of studies in which cortisol reactivity groups were compared based on the rate of externalizing behavior ($r = -.04$, $p = .70$; $Q[1,27] = .00$, $p = .99$).

Two of the subsets based on different types of externalizing behavior were significant but the difference among the effect sizes was not (Tab. 4). Similar to the set of studies on basal cortisol, the combined effect size was significant for the ''other'' subset containing studies that investigated anger and disinhibition ($r = -.09$, $p < .05$). In addition, the effect size was significant within the set of four studies on DBD ($r = -.18$, $p < .05$).

# DISCUSSION

Overall, our meta-analyses showed that there was a small but significant relation between basal levels of cortisol and externalizing behavior, whereas cortisol reactivity was not consistently associated with externalizing behavior. The relation between cortisol reactivity and behavior was only significant in small subsets of studies assessing DBD and other types of externalizing behavior (disinhibition and anger) and in the subset in which cortisol data were transformed. The effect size we found for basal cortisol and externalizing behavior is lower than often assumed in the literature. For example, Van Goozen et al. (2007) also computed effect sizes for studies investigating the relation between cortisol and antisocial behavior. They concluded that the mean effect size ($d$) was $-.40$, which is significantly higher than our finding (in our meta-analysis the overall correlation of $-.05$ would be equivalent to $d = -.10$, 95% CI $= -.19$, $-.003$). However, they included only 19 studies in their analysis (26% of our studies) and they did not investigate moderators of the relation between cortisol and antisocial behavior. In addition, their focus was on persistent antisocial behavior and they did not include studies with preschoolers. As a result, their sample overlaps to a great extent with our clinical set of studies ($k = 22$) in which a somewhat stronger effect size was found ($r = -.10$, equivalent to $d = -.20$).

## The Age Effect

The only significant moderator of the relation between cortisol and externalizing behavior in our meta-analysis on basal cortisol and externalizing behavior was the age of

**Table 4. Meta-Analytic Results of Studies Relating Cortisol Reactivity and Externalizing Behavior**

| Characteristics | *k* | *n* | *r* | 95% CI | $Q^a$ | *p* |
|---|---|---|---|---|---|---|
| Total set | 29 | 2,601 | −.04 | −.11, .02 | 65.87 | .00 |
| Sample | | | | | | |
| Clinical | | | | | .10 | .75 |
| No | 20 | 2,139 | −.05 | −.12, .02 | 42.07** | |
| Yes | 9 | 462 | −.02 | −.19, .14 | 22.63** | |
| Age[b] | | | | | .14 | .93 |
| 0–5 years | 5 | 445 | −.08 | −.22, .06 | 8.49 | |
| 5–12 years | 12 | 1,282 | −.06 | −.14, .01 | 18.23 | |
| 12–19 years | 9 | 678 | −.04 | −.18, .10 | 20.68** | |
| Broad | 3 | 186 | −.14 | −.27, .51 | | |
| Gender | | | | | .88 | .64 |
| Mainly boys | 12 | 1,340 | −.04 | −.12, .04 | 17.91 | |
| Mixed | 11 | 781 | −.02 | −.16, .11 | 33.54** | |
| Only girls | 6 | 480 | −.12 | −.26, .04 | 12.56* | |
| Study design | | | | | | |
| Aggression observed? | | | | | .70 | .40 |
| No | 22 | 1,882 | −.06 | −.15, .02 | 55.65** | |
| Yes | 7 | 719 | −.01 | −.11, .09 | 9.84 | |
| Number of cortisol samples | | | | | 1.53 | .46 |
| 0 pre, ≥1 post | 4 | 791 | −.10 | −.20, .004 | 5.33 | |
| 1 pre, 1 post | 16 | 1,293 | −.01 | −.10, .08 | 35.92** | |
| ≥1 pre and ≥post | 9 | 517 | −.05 | −.20, .10 | 21.65** | |
| Setting cortisol assessment[b] | | | | | | |
| Without peers | 26 | 2,482 | −.04 | −.11, .02 | 56.98** | |
| With peers | 3 | 119 | −.10 | −.46, .30 | 8.86** | |
| Time of cortisol sampling | | | | | 2.14 | .34 |
| Morning | 6 | 1,126 | −.07 | −.14, .01 | 7.40 | |
| (After)noon | 16 | 972 | −.08 | −.19, .04 | 46.07** | |
| Varied | 7 | 503 | .04 | −.09, .16 | 10.83 | |
| Stressor provoking aggression? | | | | | .43 | .51 |
| No | 25 | 2,492 | −.03 | −.10, .03 | 54.58** | |
| Yes | 4 | 109 | −.15 | −.47, .20 | 8.95* | |
| Type of stressor | | | | | 1.88 | .17 |
| Weak | 18 | 1,796 | −.01 | −.09, .07 | 46.61** | |
| Strong | 11 | 805 | −.10 | −.21, .002 | 18.55 | |
| Pretest included in analysis? | | | | | 1.23 | .27 |
| Yes | 25 | 1,810 | −.03 | −.10, .05 | 59.14** | |
| No | 4 | 791 | −.10 | −.20, .004 | 5.33 | |
| Cortisol measure[b] | | | | | | |
| Saliva | 26 | 2,511 | −.06 | −.12, .01 | 60.19** | |
| Plasma | 3 | 90 | .13 | −.12, .35 | 2.79 | |
| Oral stimulants used? | | | | | .11 | .75 |
| No | 21 | 2,288 | −.06 | −.12, .01 | 41.11** | |
| Yes | 5 | 223 | −.11 | −.40, .20 | 18.12** | |
| Cortisol data transformed? | | | | | .84 | .36 |
| No | 18 | 1,082 | −.01 | −.12, .10 | 51.12** | |
| Yes | 11 | 1,519 | −.07* | −.13, −.01 | 13.19 | |
| Covariates used in analyses? | | | | | .30 | .54 |
| No | 24 | 1,794 | −.06 | −.13, .02 | 51.13** | |
| Yes | 5 | 807 | −.01 | −.14, .13 | 14.10* | |
| Comparison of cortisol reactivity groups? | | | | | .00 | .99 |
| No | 23 | 2,315 | −.05 | −.11, .02 | 51.84** | |
| Yes | 6 | 286 | −.04 | −.26, .18 | 13.81* | |

(*Continued*)

**Table 4.** (***Continued***)

| Characteristics | *k* | *n* | *r* | 95% CI | $Q^a$ | *p* |
|---|---|---|---|---|---|---|
| Behavior[b] | | | | | 7.26 | .12 |
| Externalizing | 4 | 543 | .03 | −.05, .12 | 1.78 | |
| Aggression | 15 | 973 | −.03 | −.15, .10 | 47.71** | |
| DBD | 4 | 151 | −.18* | −.34, −.01 | 3.51 | |
| ADHD | 2 | 170 | −.04 | −.26, .18 | 2.17 | |
| Other | 4 | 764 | −.09* | −.16, −.02 | 2.66 | |

*Note*: *k*, number of studies; *n*, total number of participants; CI, confidence interval.

Statistics for the moderators ''research design'' and ''comorbid with internalizing'' are not given since only one reactivity study had a nonconcurrent research design and no studies provided data on comorbid internalizing problems.

*$p < .05$.

**$p < .01$.

[a]*Q* statistic for moderator stands for effect of contrasts (df = number of subgroups − 1), *Q* statistic for subgroup stands for homogeneity (df = $k - 1$).

[b]One or more of the subgroups consist(s) of less than four studies. Therefore, this/these group(s) was/were excluded from the contrast analyses, or in case of only two subsets, the effect of this moderator could not be tested.

the children. The association between cortisol and externalizing behaviors in the preschool subset was significantly different from the one in the school-age subset of studies. Higher levels of externalizing behavior were associated with higher basal levels of cortisol (hyperactivity) in preschoolers, and with lower basal levels of cortisol (hypoactivity) in school-aged children.

These contrasting findings may be explained along several lines of reasoning. The association between higher basal levels of cortisol and higher levels of externalizing behavior at an early age may be due to a common antecedent factor. Substantial levels of stress early in life or even before birth are associated with the development of externalizing behavior (for a review, see McBurnett et al., 2003) and may result in higher basal levels of cortisol, in particular higher evening levels (Gunnar & Cheatham, 2003). Essex, Klein, Cho, and Kalin (2002) investigated salivary cortisol levels of preschoolers in relation to maternal levels of stress in a longitudinal study. They found that exposure to maternal stress beginning in infancy in combination with high levels of concurrent maternal stress predisposed 4-year-old children to increased HPA functioning. The effect of early stress on the development of problem behavior may also be mediated by HPA axis functioning. For example, Huizink, Mulder, and Buitelaar (2004) concluded in their review that prenatal stress may result in general susceptibility to psychopathology in rodents and nonhuman primates by early programming of, for instance, functioning of the HPA axis. It is likely that this animal model is, at least partially, applicable to humans; in fact, there is some evidence that supports this model in humans (Huizink et al., 2004). The development of altered HPA axis functioning and problem behavior may well be a bidirectional or transactional process. According to the transactional perspective (Sameroff, 1975), child and parent behavior are mutually influencing factors. Problem behavior of children may be a source of parental stress, potentially leading parents to use harsh and inconsistent discipline (Prior, Smart, Sanson, Pedlow, & Oberklaid, 1992). Children with conduct problems have indeed been found to be subjected to more harsh punishment and inconsistent discipline than other children (Patterson, Reid, & Dishion, 1992). This, in turn, may result in higher levels of stress for the child and consequently affect HPA axis functioning.

If high levels of stress continue to exist for an extensive period of time, or in other words in case of allostatic load, the HPA axis may downregulate, resulting in lower levels of basal cortisol or hypoactivity (Fries, Hesse, Hellhammer, & Hellhammer, 2005; Gunnar & Vazquez, 2001). Results from animal studies also show that rats that were exposed to a prolonged period of chronic stress showed a hyperreactive HPA axis during the 3-week stress period and blunted corticosterone levels 2 weeks after termination of the stressor (Murison et al., unpublished data discussed in Fries et al., 2005). Similar results were presented in a recent meta-analysis by Miller, Chen, and Zhou (2007). These authors showed that cortisol levels were negatively related to time since onset of the stressor. In line with this, our results indicate that between the ages of 5 and 12 years lower levels of cortisol (hypoactivity) were associated with higher levels of externalizing behavior. Thus, children who experienced high levels of stress during development are likely to show high levels of externalizing behavior, and may have an elevated level of cortisol in early childhood, resulting in a down-regulated HPA axis producing lower levels of cortisol at school age.

The association of lower levels of cortisol with higher levels of externalizing behavior in school-aged children might also be partly explained or strengthened by mechanisms described in the sensation seeking and fearlessness hypotheses. Children with low cortisol levels

may be underaroused. This is considered to be an unpleasant physiological state and therefore, individuals with low arousal levels seek out stimulation (e.g., by showing antisocial behavior) in order to raise their arousal levels (Zuckerman, 1979). Additionally, children with low basal levels of cortisol may have low levels of fear (Raine, 1996). Because they do not (or to a lesser extent) experience the emotion of fear, they may not experience the consequences of their aggressive behavior (e.g., getting punished for acting aggressively, or seeing someone get hurt as a result of the child's aggressive behavior) as negative or aversive. Therefore, they may not connect negative consequences to their aggressive actions. They are more likely to engage in physical fights or other types of externalizing behavior because they do not fear the negative consequences of their actions.

Furthermore, the opposite direction of the relation between basal levels of cortisol and externalizing behavior in preschoolers and school-aged children may be due to developmental differences in externalizing behavior. Externalizing behaviors such as aggression are more normative in early childhood (Alink, Mesman, et al., 2006; Tremblay, 2002, 2003) and may reflect a different type of behavior at this age than in school-aged children. It may be that externalizing behaviors in early and middle childhood have different ontologies. This idea is in line with the developmental findings described by Beauchaine (2001) in his review on autonomic nervous system functioning and psychopathology. Several studies have found that vagal tone predicts behavioral reactivity and negative emotionality in infancy but is related to positive emotionality and social competence in later childhood. Beauchaine, using a developmental framework to interpret these findings, states that vagal tone is related to competent emotional expression and active engagement with the environment at all ages. The meaning of different behaviors changes with development and therefore, the relation between various biological measures (autonomic nervous system or HPA axis activity) may change as well. This concept suggests the need for developmental research and careful interpretation of findings using a developmental framework. Alternatively, it may be that especially children with externalizing problems that persist from preschool onward account for the effect at school age. In our meta-analysis however, there were no studies on clinical levels of externalizing behavior in preschoolers. Hence, we could not test whether normative and clinical levels of externalizing behavior were differentially related to cortisol in preschoolers.

No relation between basal cortisol and externalizing behavior was found in studies investigating adolescents. This may partly be due to the fact that adolescence is a period of brain reorganization (Sisk & Zehr, 2005) which may (temporarily) influence the relation between hormones and behavior. Another possibility is that the influence of social factors, such as peer groups, increases during adolescence and that these factors overrule the relation with cortisol. Nevertheless, the nonsignificant relation between cortisol and externalizing behavior is an interesting finding that calls for more research in this developmental period.

## Limitations and Recommendations for Further Research

It is important to note that externalizing problems represent a heterogeneous set of behaviors. Even the different subtypes of externalizing behaviors that were distinguished in our analyses may be heterogeneous categories in which behaviors with different origins and consequences can be found. Part of the heterogeneity may be due to comorbidity with other types of emotional and behavior problems, which is highly present in childhood (Caron & Rutter, 1991). This behavioral heterogeneity may well account for the modest effect size that we found in the total set of studies. In testing heterogeneity of externalizing behavior problems we encountered three problems. First, many studies did not investigate the co-occurrence of other behavior and emotional problems. Second, due to the relatively small number of studies in some categories (e.g., ''pure'' ADHD, delinquency) we were forced to combine several categories which hampers interpretation of the results. Third, there were only two effect sizes on the combination of internalizing and externalizing problems (Klimes-Dougan et al., 2001), and as a result, the effect of the presence of internalizing problems on the relation between externalizing problems and cortisol could not be tested.

Furthermore, it may be important to consider whether the externalizing behavior is of a proactive or reactive type. There is evidence that these types are differentially related to basal levels of cortisol, with the reactive or defensive type being related to higher levels of cortisol and the proactive or offensive type related to lower cortisol levels (see also Lopez et al., 2004; Van Bokhoven et al., 2005). Unfortunately, we were unable to test this differential relation in our meta-analyses, because most often the exact behaviors that were measured and the contexts in which they were assessed were not clearly documented. It is however important to differentiate between these types in future research.

A limitation that specifically applied to the meta-analysis concerning cortisol reactivity and externalizing behavior is the relatively small number of studies reporting on this topic. In addition, different types of stressors were used that often did not result in cortisol increase in the total group. Eleven of the studies used a strong stressor (including outcome uncontrollability and

social-evaluative threat). In this subset the relation between cortisol reactivity and externalizing behavior was near-significant ($r = -.10$, $p = .054$), indicating that when a stressor is strong enough to elicit a stress response in the total group, a relation between externalizing behavior and cortisol reactivity may be found. However, the criteria of outcome uncontrollability and social-evaluative threat as posed by Dickerson and Kemeny (2004) apply to adults and may not be as suitable for children. Indeed, some studies using these types of stressors with children did not find a stress response at all (e.g., Maldonado, Cortes, Baena, & Trianes, 2006). There is accumulating evidence for the existence of a stress hyporesponsivity period that emerges in the course of the first year of life and extends throughout childhood (see Gunnar & Fisher, 2006; Gunnar & Quevedo, 2007). During this period the HPA axis does not respond as much to stressors as it does in older individuals. Therefore, it may be difficult to find laboratory situations that provoke large increases in cortisol during the childhood years (Gunnar & Fisher, 2006; Gunnar & Quevedo, 2007).

Furthermore, it is likely that some children with high levels of externalizing behavior would be taking medications prescribed to control their behavior problems (e.g., methylphenidate or Ritalin), in particular in a clinical setting. It has been shown that these medications can influence cortisol levels (Hibel, Granger, Cicchetti, & Rogosh, 2007). Unfortunately, the medication status of the participants in a study was rarely documented (e.g., see McBurnett et al., 2005) and therefore it was not possible to include this as a moderating variable in our study. It may be that the use of (undocumented) medications reduces the possibility to detect the relation between externalizing behavior and cortisol. We recommend careful documentation of the medication status of the participants in studies investigating biomarkers, in order to be able to examine and control for the effect of medication.

The current meta-analyses focused on the direct relation between cortisol levels and externalizing behavior, without taking environmental moderators into account. A direct relation between cortisol and externalizing behavior may, however, be only part of the association between this neurobiological factor and its behavioral concomitant. Current theorizing strongly emphasizes the interplay between neurobiology and behavioral development, dependent on the specific environmental niches in which the organism develops (Belsky, 2005; Rutter, 2006). To date, empirical studies addressing these issues are rare, and their numbers insufficient to allow for conducting a meta-analysis. Our meta-analytic work might be considered the bench-mark needed to evaluate additional explanatory power of studies examining the interaction between biological and social factors.

## CONCLUSION

The results of our meta-analyses show no significant relation between cortisol reactivity and externalizing behavior and a modest association between basal cortisol levels and externalizing behavior. Only a small portion of the variance in externalizing behavior is explained by cortisol levels. Other (genetic, biological, and social) factors may offer stronger explanations of externalizing behavior. It is also very plausible that a combination of these factors and/or the interaction between several environmental and biological factors may be a better predictor of externalizing behavior. In future studies more attention should be paid to the interaction between environmental factors and the functioning of the stress system. It may well be that hypo(re)activity of the HPA axis leads to antisocial behavior when particular environmental factors such as harsh parenting or a criminal neighborhood are present, whereas in more positive environments it may positively influence people's life choices. For example, people with low arousal levels may choose a profession for which low arousal levels are vital, such as bomb disposal expert or air traffic controller, when they grow up in more supporting environments (Popma & Raine, 2006). In addition, it is important to consider the fact that most studies assessed cortisol and behavior at one time point, which may result in a clear view on the concurrent relation between these constructs, but also precludes causal inferences. Mutual influences between HPA axis functioning and behavior are most likely (Susman & Ponirakis, 1997).

In sum, the overall association between cortisol and externalizing behaviors appears to be small, but we found an important age effect. Higher levels of externalizing behavior are associated with higher basal levels of cortisol (hyperactivity) in preschoolers, and with lower basal levels of cortisol (hypoactivity) in school-aged children. Longitudinal studies are needed in order to substantiate this biobehavioral switch across age and to examine its developmental mechanisms.

## REFERENCES

References marked with an asterisk indicate studies included in the meta-analyses.

Achenbach, T. M. (1991). Integrative guide for the 1991 CBCL/4-18, YSR, and TRF profiles. Burlington, VT: University of Vermont, Department of Psychiatry.

Aiken, L.S., & West, S.G. (1991). Multiple regression: Testing and interpreting interactions. Thousand Oaks, CA, US: Sage Publications, Inc.

Amaral, D. G. (2003). The amygdala, social behaviour, and danger detection. Annals of the New York Academy of Sciences, 1000, 337–347.

American Psychiatric Association. (1994). Diagnostic and statistical manual of mental disorders (4th edn). Washington DC: American Psychiatric Press.

Angold, A., Costello, E. J., & Erkanli, A. (1999). Comorbidity. Journal of Child Psychology and Psychiatry, 40, 57–87.

Alink, L.R.A., Mesman, J., Van Zeijl, J., Stolk, M.N., Juffer, F., Koot, H.M., Bakermans-Kranenburg, M.J., & Van IJzendoorn, M.H. (2006). The early childhood aggression curve: Development of physical aggression in 10- to 50-month-old children. Child Development, 77, 954–966.

*Alink, L.R.A., Van IJzendoorn, M.H., Bakermans-Kranenburg, M.J., Mesman, J., Koot, H.M., & Juffer, F. (2006). The relation between basal cortisol, cortisol reactivity, and aggressive behavior in 2-, 3-, and 4-year-olds. Unpublished manuscript.

*Auton Cuff, F. (2004). Neurophysiological, neuroendocrine, and neuropsychological correlates of aggression in aggressive rejected and low aggressive popular seventh and eighth grade children. Dissertation Abstracts International, 66(3), 1744B (UMI No. 3168822).

*Azar, R., Zoccolillo, M., Paquette, D., Quiros, E., Baltzer, F., & Tremblay, R. E. (2004). Cortisol levels and conduct disorder in adolescent mothers. Journal of the American Academy of Child and Adolescent Psychiatry, 43, 461–468.

Bakermans-Kranenburg, M.J., Van IJzendoorn, M.H., & Juffer, F. (2003). Less is more: Meta-analyses of sensitivity and attachment interventions in early childhood. Psychological Bulletin, 129, 195–215.

Beauchaine, T. (2001). Vagal tone, development, and Gray's motivational theory: Toward an integrated model of autonomic nervous system functioning in psychopathology. Development and Psychopathology, 13, 183–214.

Belsky, J. (2005). The developmental and evolutionary psychology of intergenerational transmission of attachment. In C. S. Carter, & L. Ahnert (Eds.), Attachment and bonding: A new synthesis. Cambridge, MA: MIT Press.

*Birmaher, B., Rabin, B. S., Garcia, M. R., Jain, U., Whiteside, T. L., Williamson, D. E., Alshabbout, M., Nelson, B. C., Dahl, R. E., & Ryan, N. D. (1994). Cellular-immunity in depressed, conduct disorder, and normal adolescents: Role of adverse life events. Journal of the American Academy of Child and Adolescent Psychiatry, 33, 671–678.

*Blair, C., Granger, D., & Razza, R. P. (2005). Cortisol reactivity is positively related to executive function in preschool children attending head start. Child Development, 76, 554–567.

Borenstein, M., Rothstein, D., & Cohen, J. (2005). Comprehensive Meta-Analysis: A computer program for research synthesis [Computer software]. Englewood, NJ: Biostat.

*Çakoloz, B., Akay, A. P., & Böber, E. (2005). Assessment of plasma cortisol level in prepubertal boy with attention deficit hyperactivity disorder. Bulletin of Clinical Psychopharmacology, 15, 158–164.

Caron, C., & Rutter, M. (1991). Comorbidity in child psychopathology: Concepts, issues and research strategies. Journal of Child Psychology and Psychiatry, 32, 1063–1080.

Chrousos, G. P., & Gold, P. W. (1992). The concepts of stress and stress system disorders: Overview of physical and behavioral homeostasis. Journal of the American Medical Association, 267, 1244–1252.

Cicchetti, D. (2002). The impact of social experience on neurobiological systems: Illustration from the constructivist view of child maltreatment. Cognitive Development, 17, 1407–1428.

*Cicchetti, D., & Rogosch, F. A. (2001). The impact of child maltreatment and psychopathology on neuroendocrine functioning. Development and Psychopathology, 13, 783–804.

Cicchetti, D., & Walker, E. (2003). Neurodevelopmental mechanisms in psychopathology. New York: Cambridge University Press.

*Cooper-Fenske, C., Gardner, W., & Pajer, K. (2006). Adolescent girls with conduct disorder: HPA axis reactivity in response to psychological stress. Journal of Adolescent Health, 38, 145.

Cummings, E. M., Davies, P. T., & Campbell, S. B. (2000). Developmental psychopathology and family process: Theory, research, and clinical implications. New York: The Guilford Press.

*Dabbs, J. M., Jurkovic, G. J., & Frady, R. L. (1991). Salivary testosterone and cortisol among late adolescent male-offenders. Journal of Abnormal Child Psychology, 19, 469–478.

*De Haan, M., Gunnar, M. R., Tout, K., Hart, J., & Stansbury, K. (1998). Familiar and novel contexts yield different associations between cortisol and behavior among 2-year-old children. Developmental Psychobiology, 33, 93–101.

De Kloet, E. R. (1991). Brain corticosteroid receptor balance and homeostatic control. Frontiers in Neuroendocrinoly, 12, 95–164.

De Kloet, E. R., Joëls, M., & Holsboer, F. (2005). Stress and the brain: From adaptation to disease. Nature Reviews Neuroscience, 6, 463–475.

*DeRose, L. M. (2005). Adjustment during the transition to puberty in black and white girls. Dissertation Abstracts International, 66(5), 2852B (UMI No. 3174776).

Dickerson, S. S., & Kemeny, M. E. (2004). Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. Psychological Bulletin, 130, 355–3391.

*Dmitrieva, T. N., Oades, R. D., Hauffa, B. P., & Eggers, C. (2001). Dehydroepiandrosterone sulphate and corticotropin levels are high in young male patients with conduct disorder: Comparisons for growth factors, thyroid and gonadal hormones. Neuropsychobiology, 43, 134–140.

Duval, S., & Tweedie, R. (2000a). A nonparametric ''trim and fill'' method for accounting for publication bias in meta-analysis. Journal of the American Statistical Association, 95, 89–98.

Duval, S., & Tweedie, R. (2000b). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics, 56, 455–463.

Edwards, S., Clow, A., Evans, P., & Hucklebridge, F. (2001). Exploration of the awakening cortisol response in relation to diurnal cortisol secretory activity. Life Sciences, 68, 2093–2103.

*Essex, M. J., Klein, M. H., Cho, E., & Kalin, N. H. (2002). Maternal stress beginning in infancy may sensitize children

to later stress exposure: Effects on cortisol and behavior. Biological Psychiatry, 52, 776–784.

Fries, E., Hesse, J., Hellhammer, J., & Hellhammer, D. H. (2005). A new view on hypocortisolism. Psychoneuroendocrinology, 30, 1010–1016.

*Fulgham, L. (2003). Effects of videogame play in boys: An examination of adrenocortical activity and behavior. Dissertation Abstracts International, 64(02), 983B (UMI No. 3079297).

*Gerra, G., Zaimovic, A., Avanzini, P., Chittolini, B., Giucastro, G., Caccavari, R., Palladino, M., Maestri, D., Monica, C., Delsignore, R., & Brambilla, F. (1997). Neurotransmitter-neuroendocrine responses to experimentally induced aggression in humans: Influence of personality variable. Psychiatry Research, 66, 33–343.

*Gerra, G., Zaimovic, A., Giucastro, G., Folli, F., Maestri, D., Tessoni, A., Avanzini, P., Caccavari, R., Bernasconi, S., & Brambilla, F. (1998). Neurotransmitter-hormonal responses to psychological stress in peripubertal subjects: Relationship to aggressive behavior. Life Sciences, 62, 617–625.

Goodyer, I. M. (2002). Social adversity and mental functions in adolescents at high risk of psychopathology: Position paper and suggested framework for future research. British Journal of Psychiatry, 181, 383–386.

*Gordis, E. B., Granger, D. A., Susman, E. J., & Trickett, P. K. (2006). Asymmetry between salivary cortisol and alpha-amylase reactivity to stress: Relation to aggressive behavior in adolescents. Psychoneuroendocrinology, 31, 976–987.

*Granda, D. (1982). Aggression in preschool children viewed as a function of the 24-hour adrenocortical rhythm. Dissertation Abstracts International, 42(11), 4610B (UMI No. 8208067).

*Granger, D. A., Serbin, L. A., Schwartzman, A., Lehoux, P., Cooperman, J., & Ikeda, S. (1998). Children's salivary cortisol, internalising behaviour problems, and family environment: Results from the Concordia Longitudinal Risk Project. International Journal of Behavioral Development, 22, 707–728.

*Granger, D. A., Stansbury, K., & Henker, B. (1994a). Preschoolers behavioral and neuroendocrine responses to social challenge. Merrill-Palmer Quarterly, 40, 190–211.

*Granger, D. A., Weisz, J. R., & Kauneckis, D. (1994b). Neuroendocrine reactivity, internalizing behavior problems, and control-related cognitions in clinic-referred children and adolescents. Journal of Abnormal Psychology, 103, 267–276.

*Grayson, R. H. (2001). Physiological responsivity in aggressive and non-aggressive pre-pubertal children. Dissertation Abstracts International, 62(12), 5963B (UMI No. 3037402).

Gunnar, M. R., & Cheatham, C. L. (2003). Brain and behavior interface: Stress and the developing brain. Infant Mental Health Journal, 24, 195–1211.

Gunnar, M. R., & Donzella, B. (2002). Social regulation of the cortisol levels in early human development. Psychoneuroendocrinology, 27, 199–220.

Gunnar, M. R., & Fisher, P. A. (2006). Bringing basic research on early experience and stress neurobiology to bear on preventive interventions for neglected and maltreated children. Development and Psychopathology, 18, 651–677.

Gunnar, M. R., & Quevedo, K. (2007). The neurobiology of stress and development. Annual Review of Psychology, 58, 145–173.

*Gunnar, M. R., Sebanc, A. M., Tout, K., Donzella, B., & Van Dulmen, M. M. H. (2003). Peer rejection, temperament, and cortisol activity in preschoolers. Developmental Psychobiology, 43, 346–358.

*Gunnar, M., Tout, K., De Haan, M., Pierce, S., & Stansbury, K. (1997). Temperament, social competence, and adrenocortical activity in preschoolers. Developmental Psychobiology, 31, 65–86.

Gunnar, M., & Vazquez, D. M. (2001). Low cortisol and a flattening of expected daytime rhythm: Potential indices of risk in human development. Development and Psychopathology, 13, 515–538.

*Hart, J. L. (1999). Depressive symptomatology and altered neuroendocrine activity in maltreated children. Dissertation Abstracts International, 60(11), 5774B (UMI No. 9950292).

*Hart, D., Burock, D., London, B., Atkins, R., & Bonilla-Santiago, G. (2005). The relation of personality types to physiological, behavioural, and cognitive processes. European Journal of Personality, 19, 391–407.

*Hart, J., Gunnar, M., & Cicchetti, D. (1995). Salivary cortisol in maltreated children: Evidence of relations between neuroendocrine activity and social competence. Development and Psychopathology, 7, 11–26.

Hedges, L. V., & Olkin, I. (1985). Statistical methods for meta-analysis. San Diego, CA: Academic Press.

Hibel, L. C., Granger, D. A., Cicchetti, D., & Rogosch, F. (2007). Salivary biomarker levels and diurnal variation: Associations with medications prescribed to control children's problem behavior. Child Development, 78, 927–937.

Hinshaw, S. P., Lahey, B. B., & Hart, E. L. (1993). Issues of taxonomy and comorbidity in the development of conduct disorder. Development and Psychopathology, 5, 31–49.

Holland, P. C., & Gallagher, M. (1999). Amygdala circuitry in attentional and representational processes. Trends in Cognitive Neuroscience, 3, 65–73.

*Hruschka, D. J., Kohrt, B. A., & Worthman, C. M. (2005). Estimating between- and within-individual variation in cortisol levels using multilevel models. Psychoneuroendocrinology, 30, 698–714.

Huizink, A. C., Mulder, E. J. H., & Buitelaar, J. K. (2004). Prenatal stress and risk for psychopathology: Specific effects or induction of general susceptibility? Psychological Bulletin, 130, 115–142.

*Jansen, L. M. C., Gispen-de Wied, C. C., Jansen, M. A., Van der Gaag, R. J., Matthys, W., & Van Engeland, H. (1999). Pituitary-adrenal reactivity in a child psychiatric population: Salivary cortisol response to stressors. European Neuropsychopharmacology, 9, 67–75.

Kalin, N. H., Shelton, S. E., & Davidson, R. J. (2004). The role of the central nucleus of the amygdala in mediating fear and anxiety in the primate. Journal of Neuroscience, 24, 5506–5515.

*Kariyawasam, S. H., Zaw, F., & Handley, S. L. (2002). Reduced salivary cortisol in children with comorbid

Attention deficit hyperactivity disorder and Oppositional defiant disorder. Neuroendocrinology Letters, 23, 45–48.

Karp, J., Serbin, L. A., Stack, D. M., & Schwartzman, A. E. (2004). An observational measure of children's behavioural style: Evidence supporting a multi-method approach to studying temperament. Infant and Child Development, 13, 135–158.

Keenan, K. (2000). Emotion dysregulation as a risk factor for child psychopathology. Clinical Psychology: Science and Practice, 7, 418–434.

Kirschbaum, C., & Hellhammer, D. H. (1989). Salivary cortisol in psychobiological research: An overview. Neuropsychobiology, 22, 150–169.

Kirschbaum, C., & Hellhammer, D. H. (1994). Salivary cortisol in psychoneuroendocrine research: Recent developments and applications. Psychoneuroendocrinology, 19, 313–333.

*Klimes-Dougan, B., Hastings, P. D., Granger, D. A., Usher, B. A., & Zahn-Waxler, C. (2001). Adrenocortical activity in at-risk and normally developing adolescents: Individual differences in salivary cortisol basal levels, diurnal variation, and responses to social challenges. Development and Psychopathology, 13, 695–719.

*Kruesi, M. J. P., Schmidt, M. E., Donnelly, M., Hibbs, E. D., & Hamburger, S. D. (1989). Urinary free cortisol output and disruptive behavior in children. Journal of the American Academy of Child and Adolescent Psychiatry, 28, 441–443.

Kudielka, B. M., Buske-Kirschbaum, A., Hellhammer, D. H., & Kirschbaum, C. (2004). HPA axis responses to laboratory psychosocial stress in healthy elderly adults, younger adults, and children: Impact of age and gender. Psychoneuroendocrinology, 29, 83–98.

Kudielka, B. M., & Kirschbaum, C. (2005). Sex differences in HPA axis responses to stress: A review. Biological Psychology, 69, 113–132.

Lacey, J. I. (1956). The evaluation of autonomic responses: Toward a general solution. Annals of the New York Academy of Sciences, 67, 125–163.

Lahey, B. B., McBurnett, K., Loeber, R., & Hart, E. L. (1995). Psychobiology. In G. P. Sholevar (Ed.), Conduct disorders in children and adolescents (pp. 27–44). Washington, DC: American Psychiatric Press.

Lewis, M., & Ramsay, D. S. (1995a). Developmental change in infants' responses to stress. Child Development, 66, 657–670.

Lewis, M., & Ramsay, D. S. (1995b). Stability and change in cortisol and behavioral response to stress during the first 18 months of life. Developmental Psychobiology, 28, 419–428.

Lipsey, M. W., & Wilson, D. B. (2001). Practical meta-analysis. Applied social research methods series (Vol. 49). Thousand Oaks, CA: Sage Publications, Inc.

Liu, J. H., & Wuerker, A. (2005). Biosocial bases of aggressive and violent behavior: Implications for nursing studies. International Journal of Nursing Studies, 42, 229–241.

*Locke, R. L. (2005). Cortisol relations with child temperament and behavior problems: Consideration for context. Dissertation Abstracts International, 66(12), 6950B (UMI No. 3200147).

*Loney, B. R., Butler, M. A., Lima, E. N., Counts, C. A., & Eckel, L. A. (2006). The relation between salivary cortisol, callous-unemotional traits, and conduct problems in an adolescent non-referred sample. Journal of Child Psychology and Psychiatry, 47, 30–3036.

*Lopez, N. L. (2005). Individual differences in the activation and regulation of the limbic-hypothalamic-pituitary-adrenal axis after stress: Implications for emotion regulation research. Dissertation Abstracts International, 66(10), 5687B (UMI No. 3192712).

Lopez, N., Vazquez, D. M., & Olson, S. L. (2004). An integrative approach to the neurophysiological substrates of social withdrawal and aggression. Development and Psychopathology, 16, 69–93.

*Luby, J. L., Mrakotsky, C., Heffelfinger, A., Brown, K., & Spitznagel, E. (2004). Characteristics of depressed preschoolers with and without anhedonia: Evidence for a melancholic depressive subtype in young children. American Journal of Psychiatry, 161, 1998–2004.

Lynam, D. R. (1996). Early identification of chronic offenders: Who is the fledgling psychopath? Psychological Bulletin, 120, 209–234.

*Maldonado, E. F., Cortes, A., Baena, J. F., & Trianes, M. V. (2006). Cortisol response to psychosocial stress in 5-to 7-year-old ADHD children. Journal of Psychophysiology, 20, 240.

McBurnett, K. (1989). Adrenal and gonadal correlates of child psychopathology. Dissertation Abstracts International, 51(2), 955(UMI No. 9018354).

McBurnett, K., King, J., & Scarpa, A. (2003). The hypothalamic-pituitary-adrenal system (HPA) and the development of aggressive, antisocial, and substance abuse disorders. In D. Cicchetti, & E. F. Walker (Eds.), Neurodevelopmental mechanisms in psychopathology (pp. 324–344). New York: Cambridge University Press.

*McBurnett, K., Lahey, B. B., Capasso, L., & Loeber, R. (1996). Aggressive symptoms and salivary cortisol in clinic-referred boys with conduct disorder. Annals of the New York Academy of Sciences, 794, 169–178.

McBurnett, K., Lahey, B. B., Frick, P. J., Risch, C., Loeber, R., Hart, E. L., Christ, M. A. G., & Hanson, K. S. (1991). Anxiety, Inhibition, and Conduct Disorder in Children. 2. Relation to salivary cortisol. Journal of the American Academy of Child and Adolescent Psychiatry, 30, 192–196.

McBurnett, K., Lahey, B. B., Rathouz, P. J., & Loeber, R. (2000). Low salivary cortisol and persistent aggression in boys referred for disruptive behavior. Archives of General Psychiatry, 57, 38–43.

McBurnett, K., Pfiffner, L. J., Capasso, L., Lahey, B. B., & Loeber, R. (1997). Children's aggression and DSM-III-R symptoms predicted by parent psychophothology, parenting practices, cortisol, and SES. In A. Raine (Ed.), Biosocial bases of violence (pp. 345–348). New York: Plenum Press.

*McBurnett, K., Raine, A., Stouthamer-Loeber, M., Loeber, R., Kumar, A. M., Kumar, M., & Lahey, B. B. (2005). Mood and

hormone responses to psychological challenge in adolescent males with conduct problems. Biological Psychiatry, 57, 1109–1116.

McEvoy, M. A., Estrem, T. L., Rodriguez, M. C., & Olson, M. L. (2003). Assessing relational and physical aggression among preschool children: Intermethod agreement. Topics in Early Childhood Special Education, 23, 51–61.

McEwen, B. (1998). Protective and damaging effects of stress mediators. New England Journal of Medicine, 338, 171–179.

Miller, G. E., Chen, E., & Zhou, E. S. (2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. Psychological Bulletin, 133, 25–45.

*Montagner, H., Henry, J. Ch., Lombardot, M., Benedini, M., Burnod, J., & Nicolas, R. M. (1978). Behavioural profiles and corticosteroid excretion rhythms in young children part 2: Circadian and weekly rhythms in corticosteroid excretion levels of children as indicators of adaptation to social context. In N. Blurton Jones, & V. Reynolds (Eds.), Human behaviour and adaptation (pp. 229–265). London: Taylor & Francis LTD.

*Moss, H. B., Vanyukov, M. M., & Martin, C. S. (1995). Salivary cortisol responses and the risk for substance abuse in prepubertal boys. Biological Psychiatry, 38, 547–555.

Mullen, B. (1989). Advanced basic meta-analysis. Hillsdale, NJ: Erlbaum.

*Oosterlaan, J., Geurts, H. M., Knol, D. L., & Sergeant, J. A. (2005). Low basal salivary cortisol is associated with teacher-reported symptoms of conduct disorder. Psychiatry Research, 134, 1–10.

*Pajer, K., Gardner, W., Kirillova, G. P., & Vanyukov, M. M. (2001). Sex differences in cortisol level and neurobehavioral disinhibition in children of substance abusers. Journal of Child and Adolescent Substance Abuse, 10, 65–76.

*Pajer, K., Gardner, W., Rubin, R. T., Perel, J., & Neal, S. (2001). Decreased cortisol levels in adolescent girls with conduct disorder. Archives of General Psychiatry, 58, 297–302.

Patterson, G. R., Reid, J. B., & Dishion, T. J. (1992). A social interactional approach: Antisocial boys (Vol. 4). Eugene, OR: Castilia.

*Popma, A., Jansen, L. M. C., Vermeiren, R., Steiner, H., Raine, A., Van Goozen, S. H. M., Van Engeland, H., & Doreleijers, T. A. H. (2006). Hypothalamus pituitary adrenal axis and autonomic activity during stress in delinquent male adolescents and controls. Psychoneuroendocrinology, 31, 948–957.

Popma, A., & Raine, A. (2006). Will future forensic assessment be neurobiologic? Child and Adolescent Psychiatric Clinics of North America, 15, 429–444.

Prinzie, P., Onghena, P., & Hellinckx, W. (2006). A cohort-sequential multivariate latent growth curve analysis of normative CBCL aggressive and delinquent problem behavior: Associations with harsh discipline and gender. International Journal of Behavioral Development, 30, 444–459.

Prior, M., Smart, D., Sanson, A., Pedlow, R., & Oberklaid, F. (1992). Transient versus stable behavior problems in a normative sample: Infancy to school age. Journal of Pediatric Psychology, 17, 423–443.

Putignano, P., Dubini, A., Toja, P., Invitti, C., Bonfanti, S., Redaelli, G., Zappulli, D., & Cavagnini, F. (2001). Salivary cortisol measurement in normal-weight, obese and anorexic women: Comparison with plasma cortisol. European Journal of Endocrinology, 145, 165–171.

Putnam, K., Chrousos, G. P., Nieman, L. K., & Rubinow, D. R. (2005). Sex-related differences in stimulated hypothalamic-pituitary-adrenal axis during induced gonadal suppression. Journal of Clinical Endocrinology and Metabolism, 90, 4224–4231.

Raine, A. (1996). Autonomic nervous system activity and violence. In D. M. Stoff, & R. B. Cairns (Eds.), Aggression and violence (pp. 145–168). Mahwah, NJ: Erlbaum.

Rosenthal, R. (1995). Writing meta-analytic reviews. Psychological Bulletin, 118, 183–192.

Rutter, M. (2006). Genes and behavior: Nature-nurture interplay explained. Malden, MA: Blackwell publishers.

Sameroff, A. (1975). Transactional models in early social relationships. Human Development, 18, 65–79.

Sapolsky, R. M. (2004). Why zebras don't get ulcers: A guide to stress, stress-related diseases, and coping. New York: W.H. Freeman.

Sapolsky, R. M., Romero, L. M., & Munck, A. U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocrine Reviews, 21, 55–89.

*Scarpa, A., & Kolko, D. J. (1996). Aggression in physically abused children. Annals of the New York Academy of Sciences, 794, 405–407.

*Scerbo, A. S. & Kolko, D. J., (1994). Salivary testosterone and cortisol in disruptive children: Relationship to aggressive, hyperactive, and internalizing behaviors. Journal of the American Academy of Child and Adolescent Psychiatry, 33, 1174–1184.

*Schiefelbein, V. L. (2005). Trauma/stress, pubertal timing, and antisocial behavior. Dissertation Abstracts International, 66(4), 1966B (UMI No. 3173003).

*Schulz, K. P., Halperin, J. M., Newcorn, J. H., Sharma, V., & Gabriel, S. (1997). Plasma cortisol and aggression in boys with ADHD. Journal of the American Academy of Child and Adolescent Psychiatry, 36, 605–609.

Schwartz, E. B., Granger, D. A., Susman, E. J., Gunnar, M. R., & Laird, B. (1998). Assessing salivary cortisol in studies of child development. Child Development, 69, 1503–1513.

*Shirtcliff, E. A., Granger, D. A., Booth, A., & Johnson, D. (2005). Low salivary cortisol levels and externalizing behavior problems in youth. Development and Psychopathology, 17, 167–184.

Sisk, C. L., & Zehr, J. L. (2005). Pubertal hormones organize the adolescent brain and behavior. Frontiers in Neuroendocrinology, 26, 163–174.

*Smider, N. A., Essex, M. J., Kalin, N. H., Buss, K. A., Klein, M. H., Davidson, R. J., & Goldsmith, H. H. (2002). Salivary cortisol as a predictor of socioemotional adjustment during kindergarten: A prospective study. Child Development, 73, 75–92.

*Snoek, H., Van Goozen, S. H. M., Matthys, W., Buitelaar, J. K., & van Engeland, H. (2004). Stress responsivity in children with externalizing behavior disorders. Development and Psychopathology, 16, 389–406.

*Snoek, H., Van Goozen, S. H. M., Matthys, W., Sigling, H. O., Koppeschaar, H. P. F., Westenberg, H. G. M., & Van Engeland, H. (2002). Serotonergic functioning in children with oppositional defiant disorder: A sumatriptan challenge study. Biological Psychiatry, 51, 319–325.

*Stoff, D. M., Pasatiempo, A. P., Yeung, J., Cooper, T. B., Bridger, W. H., & Rabinovich, H. (1992). Neuroendocrine responses to challenge with Dl-fenfluramine and aggression in disruptive behavior disorders of children and adolescents. Psychiatry Research, 43, 263–276.

Susman, E. J. (2006). Psychobiology of persistent antisocial behavior: Stress, early vulnerabilities, and the attenuation hypothesis. Neuroscience and Biobehavioral Reviews, 30, 376–389.

*Susman, E. J., Granger, D. A., Murowchick, E., Ponirakis, A., & Worrall, B. K. (1996). Gonadal and adrenal hormones: Developmental transitions and aggressive behavior. Understanding aggressive behavior in children. Annals of the New York Academy of Sciences, 794, 18–30.

*Susman, E. J., & Ponirakis, A. (1997). Hormones-context interactions and antisocial behavior in youth. In A. Raine, P. A. Brennan, D. P. Farrington, & S. A. Mednick (Eds.), Biosocial bases of violence (pp. 251–269). New York: Plenum Press.

Sutton, A. J., Duval, S. J., Tweedie, R. L., Abrams, K. R., & Jones, D. R. (2000). Empirical assessment of effect of publication bias on meta-analyses. British Medical Journal, 320, 1574–1577.

Tabachnik, B. G., & Fidell, L. S. (2001). Using multivariate statistics. New York: Harper & Row.

Talge, N. M., Donzella, B., Kryzer, E., Gierens, A., & Gunnar, M. R. (2005). It's not bad: Error introduced by oral stimulants in salivary cortisol research. Developmental Psychobiology, 4, 369–376.

*Tennes, K., & Kreye, M. (1985). Children's adrenocortical responses to classroom activities and tests in elementary school. Psychosomatic Medicine, 47, 451–460.

*Tout, K., De Haan, M., Campbell, E. K., & Gunnar, M. G. (1998). Social behavior correlates of cortisol activity in child care: Gender differences and time-of-day effects. Child Development, 69, 1247–1262.

Tremblay, R. E. (2002). Prevention of injury by early socialization of aggressive behavior. Injury Prevention, 8 (Suppl. 4), iv17–iv21.

Tremblay, R. E. (2003). Why socialization fails. The case of chronic physical aggression. In: B. B. Lahey, T. E. Moffitt, & A. Caspi (Eds.), Causes of conduct disorder and juvenile delinquency (pp. 182–224). New York: Guilford Press.

Tremblay, R. E., Nagin, D. S., Séguin, J. R., Zoccolillo, M., Zelazo, P. D., Boivin, M., Pérusse, D., & Japel, C. (2004). Physical aggression during early childhood: Trajectories and predictors. Pediatrics, 114, 43–50.

Tremblay, R. E., Japel, C., Perusse, D., Boivin, M., Zoccolillo, M., Montplaisir, J., & McDuff, P. (1999). The search for the age of "onset" of physical aggression: Rousseau and Bandura revisited. Criminal Behavior and Mental Health, 9, 8–23.

*Van Bokhoven, I., Van Goozen, S. H. M., Van Engeland, H., Schaal, B., Arseneault, L., Seguin, J. R., Nagin, D. S., Vitaro, F., & Tremblay, R. D. (2005). Salivary cortisol and aggression in a population-based longitudinal study of adolescent males. Journal of Neural Transmission, 112, 1083–1096.

*Van de Wiel, N. M. H., Van Goozen, S. H. M., Matthys, W., Snoek, H., & Van Engeland, H. (2004). Cortisol and treatment effect in children with disruptive behavior disorders: A preliminary study. Journal of the American Academy of Child and Adolescent Psychiatry, 43, 1011–1018.

Van Goozen, S. H. M. (2005). Hormones and the developmental origins of aggression. In: R. E. Tremblay, W. W. Hartup, & J. Archer (Eds.), Developmental origins of aggression (pp. 281–306). New York: Guilford.

Van Goozen, S. H. M., Fairchild, G., Snoek, H., & Harold, G. T. (2007). The evidence for a neurobiological model of childhood antisocial behavior. Psychological Bulletin, 133, 149–182.

*Van Goozen, S. H. M., Matthys, W., Cohen-Kettenis, P. T., Gispen-de Wied, C., Wiegant, V. M., & Van Engeland, H. (1998). Salivary cortisol and cardiovascular activity during stress in oppositional-defiant disorder boys and normal controls. Biological Psychiatry, 43, 531–539.

*Vanyukov, M. M., Moss, H. B., Plail, J. A., Blackson, T., Mezzich, A. C., & Tarter, R. E. (1993). Antisocial symptoms in preadolescent boys and in their parents—Associations with cortisol. Psychiatry Research, 46, 9–17.

Van Zeijl, J., Mesman, J., Stolk, M.N., Alink, L.R.A., Van IJzendoorn, M.H., Bakermans-Kranenburg, M.J., Juffer, F., & Koot, H.M. (2006). Terrible ones? Assessment of externalizing behaviors in infancy with the Child Behavior Checklist. Journal of Child Psychology and Psychiatry, 47, 801–810.

Watamura, S. E., Donzella, B., Kertes, D. A., & Gunnar, M. R. (2004). Developmental changes in baseline cortisol activity in early childhood: Relations with napping and effortful control. Developmental Psychobiology, 45, 125–133.

*Weizman, R., Dick, J., Gilad, I., Weitz, R., Tyano, S., & Laron, Z. (1987). Effects of acute and chronic methylphenidate administration on beta-endorphin, growth-hormone, prolactin and cortisol in children with attention-deficit disorder and hyperactivity. Life Sciences, 40, 2247–2252.

*White, B. P., & Mulligan, S. E. (2005). Behavioral and physiologic response measures of occupational task performance: A preliminary comparison between typical children and children with attention disorder. American Journal of Occupational Therapy, 59, 426–436.

*Wright, J. M. (2000). Stress responses of adolescents as a function of anger status and its concomittants. Dissertation Abstracts International, 62(10), 4811B (UMI No. 62179).

Zuckerman, M. (1979). Sensation seeking: Beyond the optimum level of arousal. Hillsdale, NJ: Erlbaum.